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AUSTRALASIAN ANNALS OF MEDICINE

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AUSTRALASIAN ANNALS OF MEDICINE

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THE SANCTITY OF LIFE

" Life is sweet, brother."

" Do you think so ? "

" Think so !—There's night and day, brother, both sweet things ; sun, moon, and stars, brother, all sweet things ; there's likewise a wind on the heath. Life is very sweet, brother ; who would wish to die ? "

" I would wish to die—— "

" You talk like a gorgio—which is the same as talking like a fool—were you a Romany Chal you would talk wiser. Wish to die indeed—A Romany Chal would wish to live for ever ! "

" In sickness, Jasper ? "

" There's the sun and the stars, brother."

" In blindness, Jasper ? "

" There's the wind on the heath, brother ; if I could only feel that, I would gladly live for ever."

GEORGE BORROW, *Lavengro.*

THE DECLARATION OF GENEVA, adopted by the World Medical Association at its meeting in Geneva in 1948, is an expression for the modern world of Hippocratic principles. An important clause reads :

> I will maintain the utmost respect for human life, from the time of conception ; even under threat I will not use my medical knowledge contrary to the laws of humanity.

This clause when it was formulated had a profound topical significance, as it was written in the shadow of a discussion of the apostasy of the German medical profession under the Nazis, but it was not new. It echoed the Oath of Hippocrates :

> I will use treatment to help the sick according to my ability and judgement, but I will never use it to injure or wrong them. I will not give poison to anyone though asked to do, nor will I suggest such a plan. Similarly I will not give a pessary to a woman to cause abortion. But in purity and in holiness I will guard my life and my art.

These are expressions of a principle of respect for human life which medicine at its best has always upheld. Moreover, they recognize that the gypsy Jasper Petulengro, in the conversation which George Borrow has recorded for us in *Lavengro*, spoke for the whole human race : " Life is sweet, brother. Who would wish to die ? " Only the unhappy few find life so bitter that they long to pluck " the rich dark clusters of the Vine of Death " hanging over the walls of a barren life. Most men, despite privation, despite sorrow, despite pain, despite frustration, cling hungrily to life. They share with living things everywhere the urge-to-live.

In Nature this urge-to-live paradoxically but inevitably scatters death in its train. As Sir Charles Sherrington has said : " Life conflicts with life, even to the death. Life feeds on life. Man's own life feeds upon other lives. Life finds its direst enemy, the planet over, is other life." Man shares in this situation, and it becomes for him something of a dilemma as his growing sense of values presses on him an increasing respect for life. Nature, it would seem, has no such values, and so knows no such dilemma. But man cannot pretend to the mindlessness of Nature, and so in his more thoughtful moods he has come to

acknowledge the idea of the sanctity of life. Living as he does in conflict with that which is predaceous in Nature, he must defend himself and, in Sherrington's words, "set himself deliberately to exterminate those lives which invade and incapacitate and destroy his own". To sensitive souls like Albert Schweitzer this is the almost intolerable dilemma, but even Schweitzer has had to come to terms with himself on this.

On the sanctity of human life reflective man is now generally agreed. Most of his enduring philosophical systems endorse it. His greatest religions insist on it, and in the Hebrew and Christian faiths it rests firmly on the recognition of man as being made in the image of God. His laws hedge it about, whether in primitive communities or high civilizations. Even when he deliberately puts it aside in a war which he has justified to himself, he tends to feel that he is divided against himself and is relieved when the war and its necessity are over.

Medicine has a peculiar responsibility in upholding the sanctity of human life. The essential role of the practising doctor is to preserve and to enhance life. Day by day he finds his patients placing their lives and welfare completely in his hands—at once a monotonous routine and a frightening honour which he must accept. It is little wonder that Saundby asserts: "Nothing should be done to warrant any suspicion that the sanctity of human life is trifled with by the medical profession." On this principle rest both the ethical structure of medicine, without which medical practice becomes a presumption, and the doctor-patient relationship, without which medical practice becomes sterile. No doubt the realization of this largely accounts for the strong opposition shown by the medical profession to the legalization of euthanasia. Presumably it was also responsible for ranging a rationalist medical peer alongside the Archbishop of Canterbury in a common opposition to the Euthanasia Bill in the House of Lords in 1936. The peer, Lord Horder, may be said to have summed up the matter from its medical aspect in one restrained sentence: "Into this matter of putting an end to life surely a new principle enters, and I submit that this principle is outside the doctor's reference." In medicine the preservation of human life must always be paramount.

That this basic view is not affected by considerations of age, race or usefulness to society, most would agree, but it can be subtly undermined. Leo Alexander, an American psychiatrist who was present in a consultant capacity at the Nuremberg trials, has stated that the whole appalling record of crimes against humanity by German doctors started with the attitude that there is such a thing as a life not worth living—a subtle shift of emphasis in the basic attitude of medical people which issued in, amongst other things, the death of 275,000 individuals in killing centres in Germany for medical reasons and of all those found to have tuberculosis in a mass survey in Poland.

Apart from the more clearcut issues of life and death, we may well ponder whether our respect for life has wider applications. Three come to mind: the manipulation or destruction of mind and personality, discrimination in rehabilitation, and misuse of human experimentation. The cold-blooded practice of brain-washing, so highly perfected in our own day, need not detain us. It is of considerable psychiatric interest, but its practice is wholly to be abhorred. On the other hand, modern psychiatry knows very powerful and far-reaching techniques for influencing the mind—surgical, pharmacological, electrical, psychological. All have been used with valuable effect and with no shadow on the integrity of the psychiatrist, but many thoughtful people are still prepared to walk softly in these fields. The idea of discrimination in rehabilitation is one that the doctors of Holland were confronted with and, though under pressure, rejected during the German occupation. Ordered to concentrate on the rehabilitation of those most likely to return to useful work, they refused to a man—not just because the idea was designed to provide maximum

resources of manpower for the use of their German overlords, but because it implied that one human being had less right to recover than another. The special circumstances of the battle-field or the war-devastated civilian community, with casualties far beyond our resources, may force on the doctor a terrible realism, but under conditions of lesser stress, and certainly in times of peace and normality, no such discrimination can be justified by any considerations of finance or convenience. The political background of the situation may be no direct concern of the doctor, but he cannot be a party to discrimination. In this order of things all men are to him equal. On the right and wrong use of human experimentation and the limitations to be placed on clinical research, responsible investigators are still finding food for serious thought. The importance of clinical research is clear, and it must very often involve human subjects. At the same time, the immediate welfare of the individual is not to be subordinated to the pursuit of knowledge for its own sake, and no one should be made a subject of experiment without his consent. Beyond this it is difficult and perhaps unprofitable to lay down firm rules, but a good conscience is never to be despised.

Acceptance of the principle of the sanctity of life will inevitably raise conflicts in the mind of the doctor who thinks honestly and is not completely lacking in sensibility. These conflicts he will resolve in accordance with his own character and resources. Beyond this, it will help him to hold the balance if he is able to see in medicine, in Schweitzer's words, the " opportunity of tasting the blessedness of being able to assist life and avert from it suffering and destruction ".

RONALD R. WINTON.

THE CASUAL ARTERIAL PRESSURE OF FIJIANS AND INDIANS IN FIJI[1]

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SUMMARY

Casual arterial blood pressure has been measured in population samples of Fijians and Indians inhabiting Fiji.

Certain features of blood pressure found in peoples of Europe and America have been found in both races. The means and standard deviations of systolic pressures rise with age. The means of diastolic pressures rise, at least to the sixth decade. Pressures rise more in females than in males. Frequency distributions of pressures are continuous and mostly show positive skewness. Each race contains subjects with markedly raised pressures.

The overall mean systolic and diastolic pressures of Fijians and Indians are similar, but pressures rise more with age in Indians than in Fijians. Differences between races in the younger groups are reduced when differences in arm circumference are taken into account. Correction for arm circumference increases the relatively higher pressures of elderly Indians.

The levels of blood pressure of Fijians and Indians are compared in detail with those reported in a London population. The pressures of Fijians, Indians and Londoners are similar up to the sixth decade. Thereafter, those of Fijians and Indians fall below those of Londoners.

This similarity of pressures up to the sixth decade in such contrasted races is emphasized, for ways in which the races differ have previously been held to account for differences in pressures between other races. The reasons for the differences in later years are discussed.

CASUAL arterial blood pressure has been measured in Britain (Hamilton *et alii*, 1954; Miall and Oldham, 1955, 1958), Norway (Bøe *et alii*, 1957) and in the United States of America (Gover, 1948; Comstock, 1957), in population samples in which bias due to exclusion of people with high pressures has been avoided. The exact levels of pressure found have varied both between and within these populations, but certain other characteristics of blood pressure are common to all. The means and variances of systolic and diastolic pressures rise with age. The rise of mean systolic and diastolic pressures with age is greater in females than in males. The frequency distributions of pressures tend to show positive skewness, with more pressures and a larger range of pressure above modal values than below them, and as Gover (1948) and Pickering (1955) have pointed out, the distributions are continuous. They do not indicate that there are within these populations two clearly separable groups of people, one with "high" pressures and one with "normal" pressures.

There have been many reports on blood pressure in non-Western peoples. They have been summarized by Kean and Hammill (1949) and reviewed by Pickering (1955) and Smirk (1957). Blood pressures recorded have often been lower than those of Western peoples, and a rise with age has not always been evident. The causes of these differences have been the subject of much speculation; in particular, differences in climate, diet and mental attitudes have been invoked to account for them. However, the interpretation of many of these reports is difficult, for data are often incomplete, circumstances and methods of measurement have varied or not been recorded, and the subjects studied have not always been representative of the general populations from which they were drawn. Furthermore, the possible influence of arm circumference on the indirect measurement of blood pressure, which was described by Ragan and Bordley in 1941, has only lately been appreciated in population surveys (Pickering *et alii*, 1954; Miall and Oldham, 1955; Whyte, 1958; Wilson, 1958).

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We set out to study the blood pressures of the two races who inhabit Fiji, the Fijians and Indians. Our main object was to discover to what extent the characteristics of blood pressure which are common to peoples in Europe and America are shared by them. We sought, too, to compare the blood pressures of two peoples who, while living in the same place, are contrasted in many ways. The indigenous Fijians are Melanesians, upon whom there has been considerable Polynesian influence. Indians were recruited for labour in large numbers over the period from 80 to 40 years ago; they came from different parts of India, but most are now Fiji-born. A further inducement to study these peoples was the impression which exists among doctors in Fiji that Indians suffer more from arterial disease and high blood pressure than do Fijians.

A preliminary visit in November, 1956, showed that a study was practicable provided that it did not burden the local administration, and the measurements were made between January and August, 1958.

METHODS

The Population Samples

Both races were subdivided into groups of those who lived in villages or rural settlements and those who did not (Table I). The latter formed a mixed group comprising inhabitants of towns and labour lines. The selection of a strictly urban group proved impracticable.

Various localities were visited, their selection depending mainly on opportunities for reaching and working in them. The approximate populations of these localities and the numbers sampled in them are shown in Table I. Within localities, certain communities were visited, and the largest possible number of subjects in them aged over 10 years was studied. When circumstances prevented study of all available people in a community, priority was given to those aged over 40 years. No exclusions were made because of pregnancy or signs of disease.

Among the outer islands visited, Gau contained the largest population. Measurements were made there during a survey undertaken by the staff of the Central Medical School, Suva, and pressures were recorded on over 99% of the Fijian population. In other outer islands visited, about 90% of the population was studied.

On the main island, many Fijian villages and Indian rural settlements were visited with a World Health Organization team evaluating previous mass treatment of yaws. Entire communities were mustered for the study of yaws, and blood pressures were measured on as many people as time permitted, in the order of their appearance before the W.H.O. team, before the team moved to the next community. When villages and settlements were visited apart from other teams, all subjects who were available and willing were studied. Overall, 30% to 50% of the Fijian population and about 4% of the Indian population of the rural areas which were visited on the main islands were studied, though in individual communities the proportion was sometimes as high as 90%.

In towns and labour lines, the choice of communities was governed by facilities being available for making measurements where people congregated. The largest part of this sample comprised employees of government departments which were selected by the Public Relations Officer as being conveniently accessible. Employees varied from university graduates to labourers. Inhabitants of labourers' quarters provided by sugar-plantation and mill owners were included in this group, as were inmates of the prison and mental hospital, and those who came voluntarily to a stall set up on three occasions in two different market places. All the people in the selected departments and institutions were studied.

The Measurement of Blood Pressure

Rural Fijians were seen in villages, rural Indians in canefields or hamlets, and inhabitants of towns and labour lines in administrative

TABLE I

Race	Group	Approximate Number by Census in Localities Visited	Sex	Number in Sample	Approximate Percentage of Local Population Sampled
Fijians	Outer islands	850	M.	772	Over 90
		1000	F.	897	90
Fijians	Main island rural districts	1000 to 1500	M.	533	30 to 50
		1000 to 1500	F.	615	40 to 60
Fijians	Towns and labour lines	3500	M.	231	6·5
		2500	F.	64	2·6
Indians	Main island rural districts	30,000	M.	1372	4·5
		25,000	F.	906	3·5
Indians	Towns and labour lines	8000	M.	708	9
		8000	F.	189	2·3

offices or institutions. There was little apparent apprehension of the procedure.

All measurements were made by the same observer (I.M.) with a single mercury manometer and an " Erka " clip-on type cuff 13 cm. wide and 29 cm. long. After subjects had rested, seated, for at least 10 minutes, the pressure was measured with the subject seated on a chair, the cuff being applied to the right arm, which was supported on a table. The pressure was read once, the appearance of sounds on auscultation being taken as the level of systolic pressure. Diastolic pressure was taken as the pressure at which muffling of sounds preceded their disappearance. Readings were recorded to the nearest 5 mm. below the observed figure. The circumference of the arm was measured to the nearest quarter inch with a tape-measure midway between the shoulder and cubital fossa.

Each subject was asked his age. Fijians and the younger Indians answered promptly and probably accurately. Older Indians were often vague about their age. An estimate was then based on the date of their arrival in Fiji and their age at the time, on the age of the eldest child, and on the opinion of other Indians and of the observer. When such estimates could be checked with records, both usually agreed within 10 years. Indian women aged over 30 years often stated their ages as 30, 40, 50, etc. In the tables and figures, subjects up to the age of 69 years are grouped in decades—10–19, 20–29, etc.—with means for each decade of 15, 25, etc. All those over age 70 years are allotted a mean age of 75 years, because ages in this range are very uncertain.

In some communities the height, weight, pulse rate and oral temperature of every subject were also recorded. These results will be reported separately.

RESULTS

The Relation of Blood Pressure to Age and Sex

The results are summarized in Table II.[1] Figure I, which illustrates them, shows that in both races mean systolic and diastolic pressures rise from the second to at least the sixth decade, and the rise is steeper in females than in males.

The pressures in the two races have been compared in a factorial type of analysis, which is set out in the appendix. The analysis is based on 50 subjects of each sex from each decade between ages 20 and 69 years in both races, the subjects having been selected from the full data by use of random numbers. Those aged under 20 years are excluded, to avoid errors due to comparing races whose patterns of growth in adolescence may differ. Those aged 70 years and over are considered separately, because they are relatively few. The analysis shows that the curves relating systolic and

[1] Detailed tables of distributions of pressures by race, sex and age may be obtained from the writers.

TABLE II

Population Samples. Arterial Pressure (mm. Hg) by Race, Sex and Age

Age (Years)	Number	Systolic		Diastolic		Number	Systolic		Diastolic	
		Mean	Standard Deviation	Mean	Standard Deviation		Mean	Standard Deviation	Mean	Standard Deviation
	Fijian Females					*Fijian Males*				
10 to 19 ..	359	115·4	11·9	74·5	11·1	352	111·0	14·0	71·6	11·1
20 to 29 ..	461	122·8	12·3	78·5	10·6	305	125·4	13·7	80·0	9·8
30 to 39 ..	317	126·7	15·4	81·4	10·7	300	124·7	13·6	81·2	10·6
40 to 49 ..	219	134·9	22·2	84·3	11·5	293	126·5	15·0	81·8	10·1
50 to 59 ..	143	143·3	26·0	84·8	12·3	163	132·9	21·8	83·0	11·9
60 to 69 ..	56	146·4	24·3	83·3	10·8	75	133·2	23·3	79·1	12·4
70 and over	21	142·1	24·8	83·8	14·9	48	135·9	17·2	80·3	12·6
Total ..	1576					1536				
	Indian Females					*Indian Males*				
10 to 19 ..	303	113·6	14·5	65·7	5·6	313	107·3	13·6	61·6	11·3
20 to 29 ..	238	117·4	12·1	72·8	8·5	402	119·5	13·1	73·5	10·8
30 to 39 ..	179	123·3	15·7	77·5	10·2	394	121·3	14·0	77·4	11·6
40 to 49 ..	200	130·9	26·0	81·3	14·7	448	126·1	18·8	79·4	13·4
50 to 59 ..	83	147·6	29·3	84·4	15·5	187	134·1	26·2	81·3	15·4
60 to 69 ..	50	151·3	32·7	86·2	17·6	179	135·9	24·1	77·9	11·2
70 and over	42	160·4	27·8	82·4	13·2	157	137·3	27·7	76·5	12·8
Total ..	1095					2080				

diastolic pressures to age in both races between the ages of 20 and 69 years are not quite linear. There are small but significant departures from linearity, which are cubic for systolic and quadratic for diastolic pressures. These departures do not vary significantly with sex or race, and so it is possible to express them as constant factors. The equations for these curves, which are shown in Figure II, are as follows :

Systolic :

Fijian male	$y=127\cdot16+0\cdot509x-0\cdot000946x^3$
Indian male	$y=127\cdot16+0\cdot743x-0\cdot000946x^3$
Fijian female	$y=134\cdot50+0\cdot953x-0\cdot000946x^3$
Indian female	$y=134\cdot50+1\cdot188x-0\cdot000946x^3$

Diastolic :

Fijian male	$y=83\cdot28-0\cdot003x-0\cdot00916x^2$
Indian male	$y=81\cdot26+0\cdot138x-0\cdot00916x^2$
Fijian female	$y=83\cdot28+0\cdot169x-0\cdot00916x^2$
Indian female	$y=81\cdot26+0\cdot308x-0\cdot00916x^2$

where y=arterial pressure
and x=(age in years)—45.

This variable is used in preference to the simple age, so that the constant term gives the average pressure as at 45 years, the coefficient of x gives, very nearly, the average rate of increase, and other terms are constant over race and sex.

The curves for systolic pressures show differences in gradient. Indian systolic pressures increase significantly more with age than do Fijian systolic pressures, and this difference between the races is the same in both sexes. The gradient is significantly greater in females than in males, and this difference is the same in both races. There is no significant difference in the mean levels of systolic pressure between the races. Females have significantly higher mean systolic pressures than males as at age 45 years.

All the curves for diastolic pressures are parabolic in form. They also show differences in gradient. Indian diastolic pressures increase significantly more with age than do Fijian diastolic pressures, and again the difference is the same for both sexes. The linear regression for Fijian males is negative, but not significantly so. The gradient is significantly greater in females than in males, and the difference is the same in both races. There is a significant difference in the mean diastolic pressure as at age 45 years between the races, Fijians having higher pressures than Indians. Because of the difference between races in gradient, however, pressures are similar in the older age groups. There is no significant difference in the mean levels of diastolic pressure between the sexes for either race.

The relationship between the pressures observed in the 70 years and over age groups and the pressures predicted by extrapolation of the curves calculated for those aged 20 to 69 years is also considered in the appendix. While the observed diastolic pressures generally agree with those predicted, the observed systolic pressures are all relatively higher, so that extrapolation from the calculated curves beyond age 69 years is not warranted.

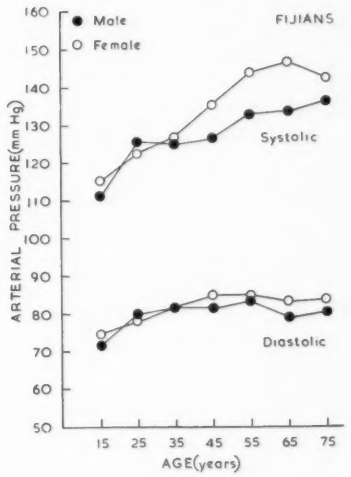

FIGURE IA

Relationship between mean systolic and diastolic pressures and age for Fijians

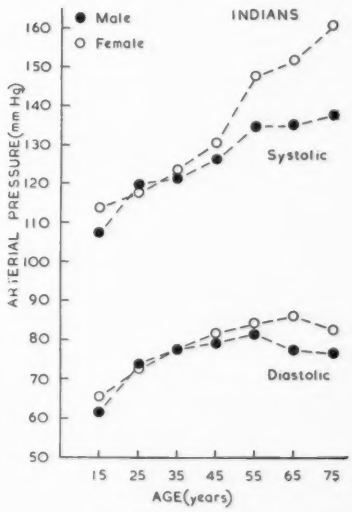

FIGURE IB

Relationship between mean systolic and diastolic pressures and age for Indians

The Distribution of Pressures

The standard deviations of pressures (Table II) are related to age in Figure III. Those of systolic pressures rise conspicuously after the fourth decade in both races and both sexes, and are greater in older Indians than in older Fijians. The standard deviations of diastolic pressures show no consistent trends, except for a steady rise in female Indians. In so far as the standard deviation describes the dispersion round a mean, these results show increasing dispersion of systolic pressures and of Indian female diastolic pressures with increasing age. However, the validity of the standard deviation as a measure of dispersion is limited when it concerns distributions which are not normal. Examination of the frequency distributions of pressures at various ages suggested that some might be positively skewed (see Figure VI), and this possibility was tested. Table III shows the results. The distributions of Indian systolic and diastolic pressures in both sexes show positive skewness in almost all decades. The same tendency is evident in Fijian systolic pressures, though the skewness is less frequently significant. It is not seen with Fijian diastolic pressures. Because of the skewness of these distributions, their standard deviations are influenced particularly by the spread of pressures towards higher values.

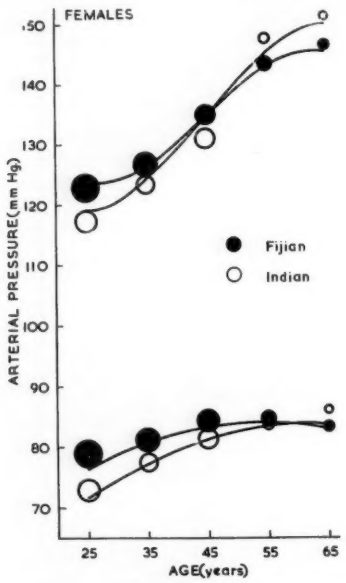

FIGURE IIA

Comparison by sex of relationship between mean systolic and diastolic pressures and age for females (Fijian and Indian). Areas of dots and circles are proportional to sample sizes in each age group. The curves are drawn from the equations in the text

The Influence of Arm Circumference

Ragan and Bordley (1941) compared intra-arterial pressure readings with those obtained with an arm cuff and auscultation. They found that in subjects with large arms the indirect readings were generally higher, and in subjects with small arms generally lower. The possibility therefore arises that differences in indirectly measured blood pressure between races may partly or wholly reflect differences in arm circumference.

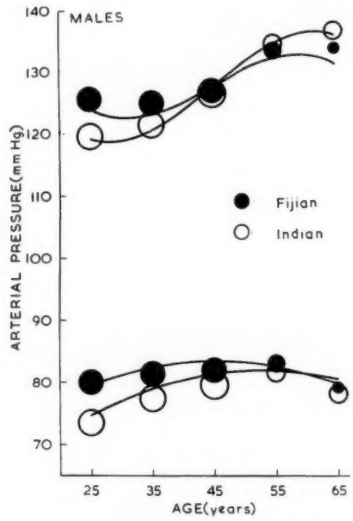

FIGURE IIB

Comparison by sex of relationship between mean systolic and diastolic pressures and age for males (Fijian and Indian). Areas of dots and circles are proportional to sample sizes in each age group. The curves are drawn from the equations in the text

The mean arm circumferences of Fijians and Indians (Table IV) are illustrated in Figure IV. In both races, arm circumferences are similarly related to sex and age, but Fijians have larger arms than Indians.

When blood pressures of both races are corrected for arm circumference, by means of the table derived from Ragan and Bordley's data by Pickering *et alii* (1954), the systolic pressures of the thinner-armed Indians are mostly raised by 5 mm. Hg. The systolic

pressures of younger Indians now approximate more closely to those of Fijians, while systolic pressures of elderly Indians are lifted further

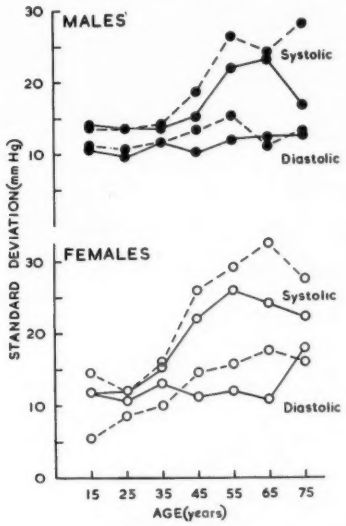

FIGURE III

Relationship of standard deviations of pressures to age. Fijian figures are joined by continuous lines, Indian figures by interrupted lines

above those of elderly Fijians. The diastolic pressures of young Fijians are lowered more than those of Indians, so that the differences in

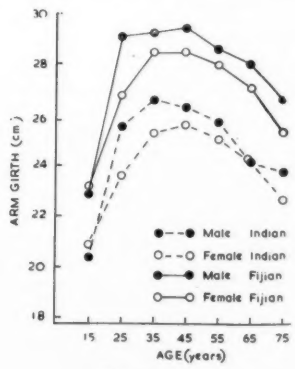

FIGURE IV

Relationship of arm circumferences and age

diastolic pressures of the two races largely disappear. The corrections do not materially change the differences between the sexes or the general relationship of pressure to age.

Comparison of Samples from Different Groups

The mean rise in pressure with age and the mean systolic and diastolic pressures at age 45 years are shown for each group within each race in Table V. These estimates are derived from pressures of subjects aged 20 to 69 years.

TABLE III

$\sqrt{b_1}$ for Blood Pressures.[1]

TABLE IIIA

Systolic Pressures

Age Group (Years)	Indian		Fijian	
	Female	Male	Female	Male
20 to 29	+1·020**	−0·038 n.s.[2]	+0·127 n.s.	+0·211 n.s.
30 to 39	+0·963**	+1·408**	+0·389 n.s.	+0·354 n.s.
40 to 49	+2·757**	+0·926**	+1·678**	+0·804**
50 to 59	+0·923**	+1·544**	+0·253 n.s.	+0·669**
60 to 69	+1·495**	+1·894**	−0·137 n.s.	+0·422 n.s.

TABLE IIIB

Diastolic Pressures

Age Group (Years)	Indian		Fijian	
	Female	Male	Female	Male
20 to 29	−0·419 n.s.[2]	+0·026 n.s.	+0·139 n.s.	−0·023 n.s.
30 to 39	+0·374 n.s.	+0·085 n.s.	−0·313 n.s.	−0·073 n.s.
40 to 49	+2·092**	+0·715**	+0·505 n.s.	−0·127 n.s.
50 to 59	+0·497 n.s.	+1·059**	+0·177 n.s.	−0·291 n.s.
60 to 69	+1·524**	+0·298 n.s.	−0·194 n.s.	+0·607*

[1] The statistic listed, $\sqrt{b_1}$, is a measure of skewness of a distribution. It has been calculated by the method of Pearson and Hartley (1956) from the samples of 50 used in the analysis of variance. A positive sign indicates positive, and a negative sign negative, skewness.

[2] n.s., Not significant; *=significant at 5% level; **=significant at 1% level.

The significantly greater mean rise in systolic pressures of Fijian males from towns and labour lines, compared with other Fijian males, reflects some unusual pressures among rather small

TABLE IV

Mean Arm Circumference (Centimetres) Compared by Race and Sex for Each Decade

Age (Years)	Females		Males	
	Fijians	Indians	Fijians	Indians
10 to 19	23·1	20·9	23·0	20·4
20 to 29	26·8	23·7	29·1	25·6
30 to 39	28·5	25·3	29·3	26·6
40 to 49	28·7	25·7	29·6	26·3
50 to 59	27·9	25·0	28·6	25·7
60 to 69	27·0	24·3	28·0	24·2
70 and over	25·3	22·7	26·6	23·8

numbers in some decades and is probably not important. The mean systolic pressure at age 45 years of Fijian women in main island rural districts is higher than that of other Fijian women. The difference is unlikely to have

TABLE V

Comparison of Population Sub-Groups in Third to Seventh Decades

Race	Group	Females				Males			
		Mean Rise of Pressures with Age (mm. Hg per Year)		Mean Pressures at 45 Years (mm. Hg)		Mean Rise of Pressures with Age (mm. Hg per Year)		Mean Pressures at 45 Years (mm. Hg)	
		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Fijians	Outer islands	0·539	0·091	131·7	82·4	0·203	0·018	128·6	81·9
Fijians	Main islands, rural districts	0·698	0·166	138·6	82·8	0·153	—0·059	128·6	80·8
Fijians	Towns and labour lines	0·528	0·138	129·0	79·0	0·570	0·052	129·3	79·4
Indians	Main islands, rural districts	0·902	0·344	135·1	80·9	0·461	0·118	127·3	77·8
Indians	Towns and labour lines	0·895	0·339	132·2	78·7	0·437	0·140	127·4	78·1

occurred by chance (P=0·01 to 0·001), it is not associated with differences in arm circumference, and it remains unexplained. Except for this discrepancy, this comparison of samples of populations from different localities fails to reveal differences within each race which might indicate the operation of different local factors affecting blood pressure. The relative homogeneity of each race with regard to blood pressure makes it unlikely that errors in sampling have distorted the overall pressure levels and their relationships to age. It is justifiable, therefore, to regard the complete sample of each race as reasonably representative of that race, and to use it for comparison with other populations.

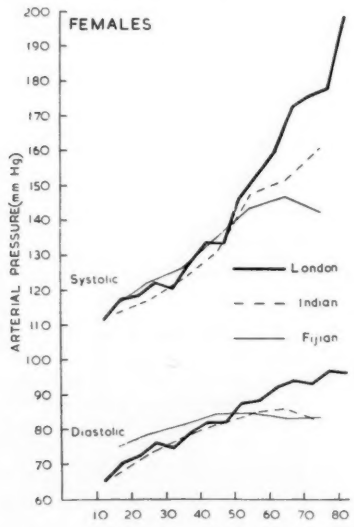

FIGURE VA

Comparison of mean systolic and diastolic pressures of females related to age between a London population (Hamilton *et alii*, 1954), Fijians and Indians

Comparison with a London Population

The pressures found by Hamilton *et alii* (1954) in London have been used, because their results are typical of surveys in Europe and America and they used the same methods of taking pressures. Figure V relates blood pressure to age in the Londoners and in Fijians and Indians in Fiji. In all three races there is resemblance in the mean systolic pressures of both sexes up to the sixth decade. Thereafter the races differ, the London population showing conspicuous rises which are not seen in Fijians or male Indians. Systolic pressures of elderly female Indians tend more towards those of elderly female Londoners. Diastolic pressures below the sixth decade are also very similar in Londoners and Indians; as has already been

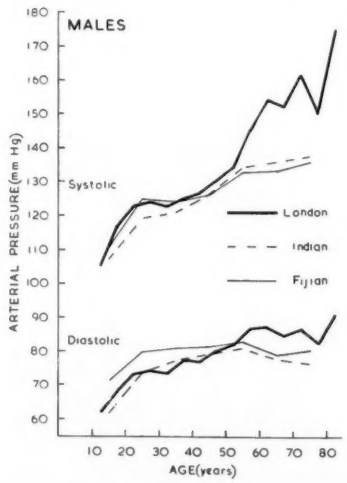

FIGURE VB

Comparison of mean systolic and diastolic pressures of males related to age between a London population (Hamilton *et alii*, 1954), Fijians and Indians

noted, the levels in Fijians are relatively high. In later years, diastolic pressures diverge like systolic pressures, those in Fijians and Indians falling below those of Londoners.

The data published by Hamilton *et alii* (1954) permit comparison of Londoners with Fijians and Indians by an extension of the factorial analysis described in the appendix. For this purpose, a sample of 50 measurements on

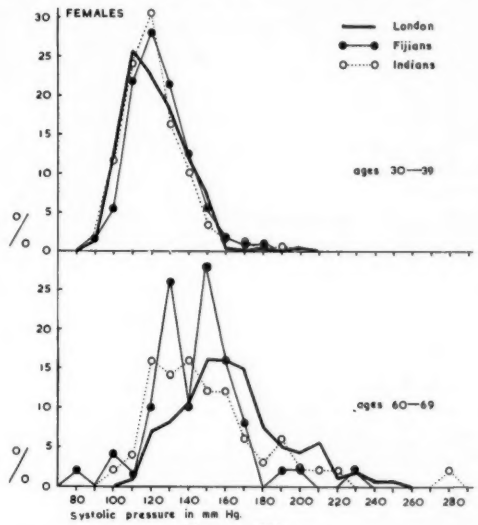

FIGURE VIA

Frequency distributions of systolic pressures of females in fourth and seventh decades of a London population (Hamilton *et alii*, 1954), Fijians and Indians

Londoners was taken at random from each of the five decades from 20 to 69 years. The equations calculated from these samples are :

Systolic :
Male :
$y = 126{\cdot}56 + 0{\cdot}176x + 0{\cdot}03571x^2 + 0{\cdot}001500x^3$
Female :
$y = 123{\cdot}76 + 0{\cdot}544x + 0{\cdot}03571x^2 + 0{\cdot}001500x^3$
Diastolic :
Male :
$y = 78{\cdot}55 + 0{\cdot}390x + 0{\cdot}00921x^2$
Female :
$y = 78{\cdot}55 + 0{\cdot}546x + 0{\cdot}00921x^2$
where, as before, y=arterial pressure and x=(age in years)—45.

The results of the main comparisons between Londoners on the one hand and Fijians and Indians on the other are as follows.

1. Pressures as at age 45 years. There is no significant difference in mean systolic or diastolic pressures between Londoners, Fijians and Indians. The difference found in Fijians and Indians between the sexes in systolic pressures is not apparent in the Londoners over this age span, though such a difference was revealed by comparing the data for Londoners of all ages (Hamilton *et alii*, 1954). This difference between races in the effect of sex on mean systolic pressures between ages 20 and 69 years appears to be due to the divergence of pressures between

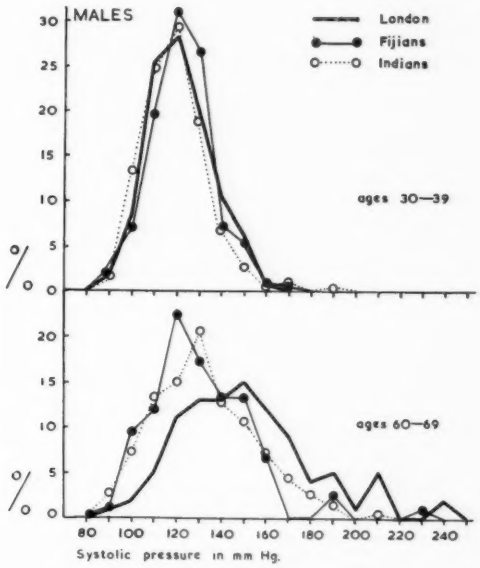

FIGURE VIB

Frequency distributions of systolic pressures of males in fourth and seventh decades of a London population (Hamiltion *et alii*, 1954), Fijians and Indians

the sexes at a later age in Londoners than in Fijians and Indians.

2. Linear slope. The rate of increase of pressures with age is significantly greater in Londoners than in Fijians and Indians. The difference between the sexes is the same in all three races.

3. Shape of the curve. The shapes of the curves relating pressures and age for Londoners differ from those for Fijians and Indians. The curves for systolic pressures contain positive cubic and diastolic pressures positive quadratic terms.

The standard deviations of systolic pressures are of similar magnitude and bear similar relationships to age in all three peoples. The standard deviations of diastolic pressures of Londoners resemble those of Indian females in rising with age.

Figure VI compares the frequency distributions of systolic pressures in the three peoples

in the fourth and seventh decades. It shows that distributions of pressures are similar in both sexes in the fourth decade. In the seventh decade in both sexes, the distribution curve for Londoners is shifted to the right, so that Londoners differ from Fijians and Indians in having fewer rather low pressures and more rather high pressures, and their modal values are higher.

Details of arm circumference were not published by Hamilton *et alii* (1954), but Dr. W. E. Miall has kindly given us measurements made during his study with Mr. P. D. Oldham in South Wales (Miall and Oldham, 1955). Assuming these to reflect arm circumference in Britain, we used them to correct the data on Londoners. The effect of correcting pressures in the three races is to cause a small rise in systolic pressures in young male Londoners relative to Fijians and Indians, and to approximate diastolic pressures in young Fijians to those of both Indians and Londoners. In older people, systolic pressures are raised in Indians, but not in Londoners. The pressures of elderly Indian women, already not far below those of London women, now resemble the latter even more closely.

DISCUSSION

Evidently certain features of blood pressure found in peoples of Europe and America are also present in two distinct races living in a group of tropical Pacific Islands. The means and standard deviations of systolic pressures rise with age. The means of diastolic pressure also rise, at least up to the sixth decade. Pressures rise more in females than in males. The frequency distributions of pressures are generally continuous, and mostly show similar tendencies to positive skewness. Each race contains a proportion of subjects with markedly raised pressures, and this proportion increases with age. These features of blood pressure are not therefore peculiar to Western civilization.

Fijians and Indians differ in regard to blood pressure mainly in the relationship of mean systolic and diastolic pressures to age. The differences, though statistically significant, are small, and in the younger age groups, and they are further reduced when account is taken of differences in arm circumference. Among elderly females, however, it is probable that an important difference exists, since the relatively higher pressures of elderly Indian women are further increased when corrections are made for arm circumference. The reasons for these higher pressures in elderly Indian women have yet to be defined. They may reflect a difference between the races in the incidence of conditions in earlier life which predispose to higher pressures. For instance, the commoner occurrence of toxæmia of pregnancy (Bell and Wills, 1955) and anæmia of pregnancy (Oldmeadow, 1956) in Indians as compared with Fijians may be relevant.

The features of blood pressure which distinguish Londoners from both races in Fiji are the rates at which mean systolic and diastolic pressures rise with age, the shapes of the curves relating pressures to age, and the means and frequency distributions of pressures in the elderly. Because of the probable effects of arm circumference on the indirect measurement of blood pressure, the differences between the relationship of pressures to age described by equations have limited meanings. It is more important to stress the similarity in means and frequency distributions of pressures between the three populations from the third to the sixth decades and the differences thereafter.

The finding that blood pressures, not only in Fijians and Indians, but also in Londoners, are so similar up to the sixth decade is particularly interesting, because many of the ways in which these three racial groups are contrasted have in the past been invoked to explain apparent differences in pressures between other races. Mental attitudes, diet, patterns of disease and climate provide examples. It would be hard to find peoples who differed more in their attitudes to life. The Fijian is generally happy-go-lucky, indolent, friendly and secure in a way of life based on centuries of chiefly authority. The Indian is striving and earnest and has found opportunity for profit and advancement, but because of the history of his race in the colony he is often socially insecure. Fijians and Indians, while rarely suffering from malnutrition, eat less than Europeans. The daily diet of Fijians contains about 44 grammes of fat, 46 grammes of protein and 476 grammes of carbohydrate (Langley, 1954), and of Indians about 40 grammes of fat, 60 grammes of protein and 360 grammes of carbohydrate (O'Loughlin and Holmes, 1954). Foodstuffs and modes of cooking differ. Salt is eaten by both races, and they both smoke cigarettes, but the amounts of either consumed are not known. The differences in climate between London and Fiji require no elaboration. The main causes of disease and death in Fijians and Indians up to the sixth decade are injuries, infections and infestations; tuberculosis, filariasis, hookworm and rheumatic fever are all common. These and the many other ways in which the peoples of Fiji, Europe and America are contrasted are

clearly consistent with remarkably similar mean levels and frequency distributions of systolic and diastolic pressures from the third to the sixth decades.

The differences in blood pressure which exist between elderly Western peoples and elderly Fijians and Indians are remarkable when contrasted with the similarities between the three populations at earlier ages. It appears that the tendency in individuals for blood pressure to increase with age (Hamilton *et alii*, 1954; Smirk, 1957) is more pronounced from middle age onwards in Western peoples than in Fijians and Indians. It is not clear what this tendency is due to, nor whether it results from the same factors in Europeans as in the inhabitants of Fiji. The factors could be environmental or genetic and mediated by physiological or pathological changes.

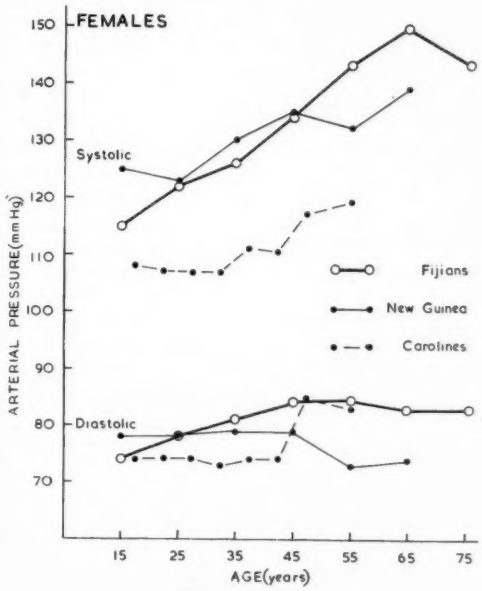

FIGURE VIIA

Comparison of systolic and diastolic pressures related to age between female Fijians, peoples of New Guinea (Whyte, 1958) and Caroline Islanders (Murrill, 1949)

There are other possible explanations for the difference in pressures between elderly Western peoples and Fijians and Indians. Such a difference would occur if those Fijians and Indians destined to develop higher pressures died selectively at earlier ages. There is no evidence to commend this suggestion. The greater incidence of higher pressures in elderly Europeans might occur if individual Fijians and Indians with higher pressures died more readily. There is some evidence that the common causes of death from high blood pressure are rare in Fijians, though probably less so in Indians. It is possible, therefore, that if deaths from high blood pressure were taken into account, the incidence of high pressures in elderly Europeans could be still greater than in Fijians of corresponding age.

Of all the possible environmental factors which might account for the differences in pressures between elderly peoples of Fiji and London, climate appears unimportant, for failure of pressures to rise steeply in the elderly is not invariable in the tropics. In the Virgin Islands,

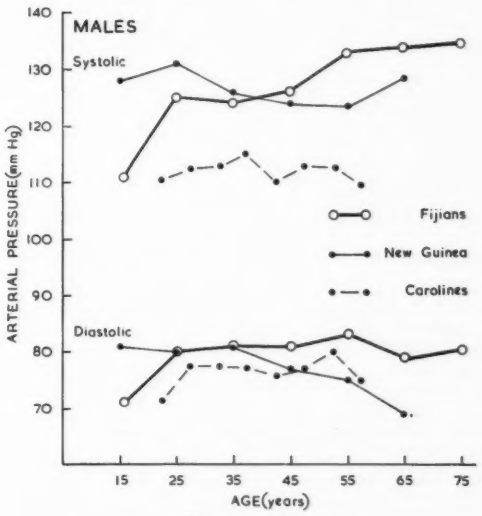

FIGURE VIIB

Comparison of systolic and diastolic pressures related to age between male Fijians, peoples of New Guinea (Whyte, 1958) and Caroline Islanders (Murrill, 1949)

which in climate and latitude resemble Fiji, the blood pressures of whites and Negroes rise in old age as in the Western peoples (Saunders and Bancroft, 1942) and there, as in America (Gover, 1948), the pressures of Negroes are higher than those of whites.

Clues to the effects of genetic and environmental factors on blood pressure may be obtained by comparing the pressures of similar racial groups in various environments. We have compared our findings on Fijians and Indians in Fiji with those reported on other Pacific Islanders (Figure VII) and on other Indians (Figure VIII). In view of the difficulties already mentioned which are inherent in these comparisons, conclusions must be tentative. The pressures

of Fijians are generally similar to those reported by Whyte (1958) for a population sample in New Guinea. Whyte estimated age and took the disappearance of sounds as the diastolic end-point. These factors, together with the relatively small numbers of subjects on which his findings were based, may contribute to such differences as exist. Like Fijians, the peoples of New Guinea are predominantly Melanesian, and their environment is in many respects similar to that of rural Fijians. Murrill (1949) recorded much lower systolic pressures at all ages and frequently lower diastolic pressures in a small sample of the inhabitants of Ponape in the Eastern Carolines. Even when allowance is made for the small numbers he studied and for differences in method, the differences between Ponapians and the peoples of Fiji and New Guinea appear to be real. Murrill considered that hookworm infestation and tuberculosis might account for the low pressures he recorded in 1947. Since both are common in Fijians in Fiji it is unlikely that they account for the difference between the two peoples. When the study was made, the Caroline Islanders had only lately been relieved of wartime life under Japanese occupation. It is important to discover whether their blood pressures have remained at the levels found in 1947, for their environment appears similar to that of rural Fijians, from whom, however, being Micronesians, they are racially distinct.

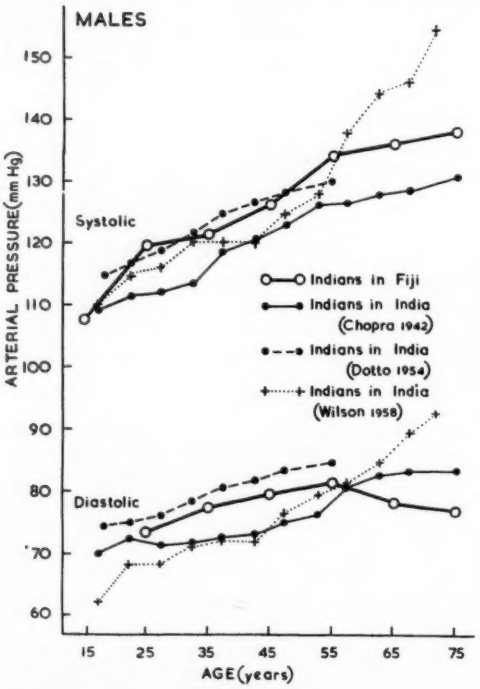

FIGURE VIII

Comparison of systolic and diastolic pressures related to age between male Indians in Fiji and in India (Chopra *et alii*, 1942 ; Dotto, 1954 ; and Wilson, 1958)

Such surveys as have been made on Indians in India have, until lately, concerned selected groups, almost exclusively male (Chopra *et alii*, 1942 ; Dotto, 1954). A relationship between blood pressure and age similar to that which we found in Indians in Fiji is apparent in both these studies (Figure VIII). The levels of pressure found by Dotto are also very similar to those which we found ; those found by Chopra *et alii* are a little lower. Wilson's (1958) recent findings on upper Assam tea-garden labourers of both sexes are, however, similar to those of Hamilton *et alii* (1954) on Londoners, the pressures rising steeply in later years. Indians separated geographically thus appear to differ among themselves in the same way as the peoples of Fiji differ from Londoners. These populations of Indians merit further detailed study, not only as regards their enrivonment, but also as regards their genetic background, for the term "Indian" comprises several different racial groups.

These comparisons between different population groups within similar races do little at present to elucidate the main question posed by our findings—namely, the reasons for the differences in blood pressure between elderly Western peoples and elderly Fijians and Indians. It remains difficult to distinguish between the consequences of inheritance, environment and different types of morbidity and mortality. The question which has been defined is nevertheless important, for attempts to answer it may reveal factors which are responsible for the more frequent occurrence of those higher pressures in Western peoples which are often associated with cardio-vascular disease.

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APPENDIX: STATISTICAL ANALYSIS OF RELATIONSHIPS BETWEEN RACE, SEX, AGE AND BLOOD PRESSURE

In the original data, for each sex and race the subjects were grouped into ten-year age-groups, with unequal numbers in the groups. Polynomial equations were required to represent the relationship of blood pressure to age in each population. To enable the various terms in the polynomial regression to be tested independently, and to facilitate comparisons between the populations, equal numbers were necessary in all groups. Random samples of 50 subjects were taken from each age group in both sexes and both races. Only the five age groups 20–29, 30–39, . . . , 60–69, were considered at this stage, since in some cases there were too few people in the 70 years and over age groups.

The analysis of variance was carried out as a $5 \times 2 \times 2$ factorial analysis, by means of the tabular method described by Bainbridge *et alii* (1956). Systolic and diastolic pressures were analysed separately. The breakdown of the analysis of variance into factors was as follows:

1. Age group. Differences between the five age groups were analysed into mean, linear, quadratic, cubic and quartic components, by means of the orthogonal polynomials listed in Fisher and Yates' tables (Fisher and Yates, 1953).

2. Sex. Averages over the two sexes, and differences between male and female, were calculated for each of the five age-group comparisons.

3. Race. The 10 pairs of results were totalled over the two races, and the difference between Indians and Fijians was calculated for each pair.

The analysis of variance is shown in Table VI.

INTERPRETATION OF THE ANALYSIS

1. Overall mean. [1] measured the overall average blood pressure. This was the mean pressure for all age groups, males and females, and Fijians and Indians.

2. Main effects. A_1, A_2, A_3 and A_4 respectively measured the linear, quadratic, cubic and quartic components of the pressure-age relationship averaged over both races and both sexes. B was the mean

difference between males and females averaged over both races and all age groups. C was the mean difference between races averaged over both sexes and all age groups.

3. Interaction. An interaction between B (or C) and one of the A terms, say A_2, measured the difference in that component, in this case quadratic, between sexes (or races). Only the linear component was expected to vary between the sexes, so that the values of BA_2, BA_3, BA_4 were used as measure of variability.

The BC interactions measured the difference, between races, in the difference between male and female average pressure.

An interaction with three terms, such as BCA_1, would have an extremely complex interpretation. However, these were not expected to be important, and were included in the error estimate.

TABLE VI

Analysis of Variance

	Systolic Pressure		Diastolic Pressure	
	Mean Square	Significance	Mean Square	Significance
[1]	17116489		6470594	
A_1	55493	**[1]	4667	**
A_2	286	n.s.[1]	2350	**
A_3	2576	**	41	n.s.
A_4	67	n.s.	12	n.s.
B	13469	**	828	n.s.
BA_1	9879	**	1471	*[1]
BA_2	91 (e)[2]		476 (e)	
BA_3	353 (e)		12 (e)	
BA_4	43 (e)		11 (e)	
C	6	n.s.	1020	*
CA_1	2749	**	973	*
CA_2	2	n.s.	43	n.s.
CA_3	29	n.s.	56	n.s.
CA_4	321	n.s.	27	n.s.
BC	250	n.s.	194	n.s.
BCA_1	23 (e)[2]		33 (e)	
BCA_2	5 (e)		173 (e)	
BCA_3	140 (e)		28 (e)	
BCA_4	754 (e)		424 (e)	
Error mean square (7 d.f.)	201·29		165·29	

[1] n.s. = not significant; * = significant at 5% level; ** = significant at 1% level. All these comparisons are based on 1, 7 degrees of freedom.

[2] (e) = included in error mean square.

INTERPRETATION OF RESULTS IN TABLE VI

Systolic Pressures

1. Average Pressure (as at 45 Years):
   - (i) B**, BC, n.s. Average pressure was higher in females than in males. This difference was the same for both races.
   - (ii) C, n.s. The average pressure did not vary between races.
2. Linear Slope:
   - (i) A_1**. Blood pressure increased with increase in age.
   - (ii) BA_1**. The rate of increase of pressure with age was greater for females than for males.
   - (iii) CA_1**. The rate of increase of pressure with age was greater for Indians than for Fijians.
3. Shape of Curve:
   - (i) A_2, n.s., A_3**, A_4, n.s. Departures from linearity in the shape of the curve were cubic in form.
   - (ii) CA_2, CA_3, CA_4, n.s. The shape of the curve was the same for Fijians as for Indians.

Diastolic Pressures

1. Average Pressure (as at 45 years):
   - (i) B, n.s. Average diastolic pressure did not vary significantly between the sexes. However, there was an indication that females had higher pressures than males.
   - (ii) C*, BC. n.s. Indian diastolic pressures were, on the average, higher than Fijian pressures. This difference was the same for both sexes.
2. Linear Slope:
   - (i) A_1**. Blood pressure increased with increase in age.
   - (ii) BA_1*. The rate of increase of pressure with age was greater for females than for males.
   - (iii) CA_1*. The rate of increase of pressure with age was greater for Indians than for Fijians.
3. Shape of Curve:
   - (i) A_2**, A_3, n.s., A_4, n.s. Departures from linearity in the shape of the curve were quadratic in form.
   - (ii) CA_2, CA_3, CA_4, n.s. The shape of the curve was the same for Fijians as for Indians.

TABLE VII

Blood Pressures in 70 Years and Over Age Groups (mm. Hg)

Race	Male				Female			
	Observed (1)	Predicted (2)	Standard Deviation (1)–(2)	t_{14}	Observed (1)	Predicted (2)	Standard Deviation (1)–(2)	t_{14}
Systolic								
Indian ..	137·32	125·06	5·94	2·06*[1]	160·36	143·45	6·99	2·42*
Fijian ..	135·94	118·02	6·04	2·97**[1]	142·14	136·41	7·73	0·74 n.s.[1]
Diastolic								
Indian ..	76·50	77·35	2·27	0·37 n.s.	82·38	82·04	2·88	0·12 n.s.
Fijian ..	80·31	75·18	2·73	1·88*	83·81	79·87	3·83	1·03 n.s.

[1] n.s. = not significant; * = significant at 5% level; ** = significant at 1% level.

DERIVATION OF EQUATIONS

Linear components, adjusted for difference in sex and race, and the significant higher order terms were calculated from the samples used for the analysis of variance. By the use of the standard orthogonal polynomial expressions, the equations given in the main part of the paper were obtained.

RESULTS FOR 70 YEARS AND OVER AGE GROUPS

The fitted curves gave the best polynomial representation of the data over the ages 20 to 69. However, this type of curve may not give valid results outside these age limits. A measure of their validity was given by the fit of the extrapolated curves to the data on those aged 70 years and over. A one-tailed t test was used, since it was expected that if the data did not fit the extrapolated curves, observed pressures would be higher than predicted, and never lower.

Table VII shows the comparison between observed and predicted mean pressures. The extrapolated curve did not give a good fit for systolic pressure, since pressures in the 70 years and over age groups would not be expected to fall markedly, and in fact did not do so. Diastolic results seemed to fit, although the difference for Indian females was significant at the 5% level.

PRIMARY PULMONARY HYPERTENSION IN EIGHT PATIENTS INCLUDING A MOTHER AND HER DAUGHTER[1]

H. FLEMING[2]

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SUMMARY

Primary or idiopathic pulmonary hypertension was until recently considered a rare disorder. Since its widespread recognition in 1957 it has become evident that, while it is uncommon, it is far from rare. The present report of eight cases seen in one year substantiates this.

The clinical picture is fairly characteristic and is described in this paper. Study of the jugular venous pulse would avoid many of the errors and delays in diagnosis. The course of the disease is one of progression at a variable rate, leading to death in right heart failure or from sudden arrhythmia. In this series the progression was rapid and often of a malignant nature.

Cardiac catheterization will confirm the diagnosis and assess the pulmonary vascular resistance. The effects of drugs on this resistance can also be studied. This is of particular importance, as there is at present no effective treatment for this disease.

Pulmonary function studies show no evidence of major disorder in the lungs. Polycythæmia and arterial desaturation are common. These are not always associated with a right-to-left shunt through a patent foramen ovale.

The increasing frequency of reports of primary pulmonary hypertension occurring in relatives suggests that congenital or geographic factors may be of importance in the pathogenesis.

PRIMARY or idiopathic pulmonary hypertension was, until recently, regarded as a rare disease. As Whitacker and Heath (1959) point out, Brenner (1935) was able to collect only 16 acceptable cases from the literature at that time, but at least 34 new cases were reported in 1957 alone. While the disease remains uncommon, it is far from rare, and it is seen not infrequently in the cardiac clinics where it is recognized. The true incidence is difficult to assess, but Wood (1956) saw 17 cases in his series of 10,000 patients with heart disease, an incidence of 0·17%. The ætiology of this disorder is quite unknown, and as Wade and Ball (1957) have pointed out, patients with various basic disorders may present in this way. Wood (1956), however, indicates that the clinical picture is sufficiently distinctive to be recognized, and this is borne out by his record of 10 such cases in which the diagnosis was confirmed at autopsy. As will be indicated in this paper, these patients are frequently considered neurotics or sufferers from gastric disorder before the true diagnosis is made.

It is the purpose of this paper to record eight cases studied at this clinic in the period of a year; seven of these were seen personally. The malignant course of the disorder will be emphasized, and its occurrence in a mother and daughter and other members of the family will be detailed.

In recent reports the earlier literature has been fully reviewed (Wade and Ball, 1957; Shepherd *et alii*, 1957; Heath *et alii*, 1959; Evans *et alii*, 1957; Chapman *et alii*, 1957; Whitacker and Heath, 1959). A detailed review will not be made here.

INCIDENCE

During the period in which these eight cases were seen, 500 cases of cardiac or suspected cardiac disease were seen at this clinic. In the previous 3500 cases, the diagnosis of primary pulmonary hypertension was made only once. It is difficult to gauge the true incidence, but it is certain that this disorder is not rare in Australia. A high incidence in young women has been reported, and in this series six out of the eight patients were young women.

PRESENTATION

Symptoms

The symptoms and associated features are shown in Table I. In Case IV the patient had no symptoms. She had been under observation since the diagnosis was made in her mother.

[1] Received on October 9, 1959.

[2] Director.

TABLE I

Clinical Details and Outcome of the Eight Cases

Case Number, Patient's Initials, Sex and Age (Years)	Age (Years) at Presentation	Dyspnœa Grade[1]	Syncope	Angina Pectoris	Right Subcostal Pain	Sensitivity to Cold	Cough	Recent Weight Loss	Fate[2]	Duration from Onset (Months)	Habitat
I: D.G.: M.: 28	28	4	−	−	+	−	−	+	D.	6	Sydney, N.S.W.
II: F.M.: F.: 37	33	2	+	+	−	+	−	−	A.	48	Longreach, Q.
III: M.S.: F.: 32	31	4	+	+	+	+	−	+	D.	18	Lake Cargelligo, N.S.W. and Sydney
IV: L.S.: F.: 10	—	0	−	−	−	−	−	−	A.	—	Lake Cargelligo, N.S.W. and Sydney
V: N.S.: M.: 30	30	4	+	−	+	+	+	+	D.	6	Orange, N.S.W.
VI: H.B.: F.: 18	15	4	+	−	+	+	+	+	D.	36	Brisbane, Q.
VII: J.D.: F.: 26	25	4	+	−	+	+	−	+	V.S.	10	Sydney, N.S.W.
VIII: N.C.: F.: 34	33	4	+	−	+	+	+	?	P.D.	12+	Melbourne, Vic., and Broken Hill, N.S.W., etc.

[1] Dyspnœa graded 0 to 4.
[2] A, alive; D, dead; P.D., presumed dead; V.S., very sick.

The presenting symptom in six of the seven patients with symptoms was dyspnœa on exertion. In several cases the dyspnœa was accompanied by lassitude and weakness, and shortly by syncope. In one patient weight loss and abdominal pain were the initial complaints, and dyspnœa was noted by the doctor. Another five patients early complained of abdominal pain. In Case III this was initially premenstrual, but in all cases it was aggravated by exertion. The mechanism of this pain appears undoubtedly to be hepatic distension.

Syncope is common on exertion, and is due to the low cardiac output with acute right ventricular failure (Howarth and Low, 1953). At a more advanced stage it may occur spontaneously, and a constant feeling of dizziness is common terminally.

Angina pectoris is in all respects of a classical type, and again is due to functional coronary ischæmia secondary to the severely restricted cardiac output (Stuckey, 1955).

Acquired sensitivity to cold is a frequent complaint. Particular difficulty is experienced in keeping the extremities warm.

Cough may be a very troublesome symptom. It is usually unproductive and is difficult to suppress. Orthopnœa and hæmoptysis did not occur, and they are unusual.

Signs

The signs (Table II) are those of pulmonary hypertension due to any cause, and are in no way specific.

Cyanosis is largely peripheral, but, as is indicated by the arterial saturation figures in Table III, there is not infrequently also a central element. Clubbing did not occur. In advanced stages the peripheral cyanosis extends more centrally, and the trunk may show a sinister appearance of blue, marble-like mottling.

In this series œdema occurred in the terminal months only. It may be associated with prolonged heart failure.

The jugular venous pressure is always raised, and the characteristic finding is a giant *a* wave (Figure I). This may be transmitted through the right ventricular trace into the pulmonary artery trace recorded at catheterization. This is well shown in Figure VI. Wood (1956) emphasizes the importance of this *a* wave in indicating that there is no alternative route for ejection from the right ventricle. In this series the height of the *a* above the sternal angle ranged from 3 to 10 cm. When tricuspid incompetence supervenes, the wave is systolic in timing. Three patients had noticed the flicking of the venous pulse in their neck before it was reported by their doctors. When there is marked elevation of the jugular venous pressure, it is commonly accompanied by pulsatile enlargement of the liver, which is usually tender.

The pulse is of small volume. In all these cases sinus rhythm was invariable. Atrial

TABLE II

Frequency of Occurrence of the Auscultatory Findings Shown Diagrammatically in Figure II

Sound	Number of Cases
Right atrial sound	4
Normal first heart sound	8
Pulmonary ejection click ..	6
Short ejection murmur	7
Accentuated P_2 (often palpable)	8
Pulmonary early diastolic murmur	2
Right ventricle third heart sound..	4

TABLE III

Cardiac Catheterization Findings

Case Number	Initials	Pulmonary Artery Pressure and Mean (mm. Hg)	Brachial Artery Pressure (mm. Hg)	B.A.—P.A.[1] Syst. Press.	Cardiac Output (Litres per Minute)	Pulmonary Vascular Resistance (Units)	Arterial Saturation (Percentage)	Effect on Pulmonary Artery Pressure or Pulmonary Vascular Resistance of			Shunt by Dye Curve
								Acetyl Choline	Reserpine	Oxygen (100%)	
I	D.G.	120/53 : 77	120/90	0	2·1	26	80	Not tried	Not tried	Not tried	Not tried
II	F.M.	80/30 : 46	115/70	35	3·0	15	88	Not tried	Not tried	Not tried	Not tried
III	M.S.	105/55 : 70	120/80	15	2·7	24	93	0	0	0	0
IV	L.S.	60/40 : 45	110/75	50	3·7	11	94	+	Not tried	+	0
V	N.S.	140/80 : 87	105/60	−35	3·0	27	93	0	0	0	0
VI	H.B.	116/70 : 80	105/75	−11	2·0	40	82	Not tried	Not tried	Not tried	Right→ left
VII	J.D.	100/60 : 75	140/105	40	2·2	32	86	0	Not tried	0	Right→ left atrial
VIII	N.C.	84/40 : 55	100/72	12	2·0	27	85	Not tried	Not tried	Not tried	Not tried
Normal subjects	—	25/10 : 15	125/78	190	5·0	2	95				

[1] Brachial artery pressure minus pulmonary pressure/systemic arterial pressure.

fibrillation may, however, supervene at a late stage.

On palpation of the chest, the hyperdynamic pulsation of the right ventricle and the pulmonary artery and the palpable closure of the pulmonary valve are characteristic.

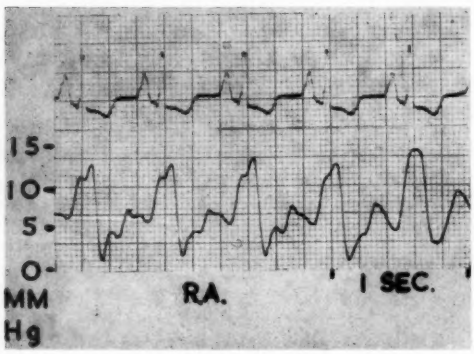

FIGURE I

Electrocardiogram lead II and right atrial pressure pulse, Case VII. The giant *a* wave measures 13 mm. Hg above the sternal angle. Note also the *P* pulmonale

The auscultatory findings are shown diagrammatically in Figure II, and their frequency is indicated in Table II. These are the auscultatory findings of pulmonary hypertension with or without right ventricular failure. The pulmonary systolic murmur is always short and soft. When tricuspid incompetence occurs, a pansystolic murmur increasing on inspiration may be present. However, with free tricuspid incompetence this may be quite unremarkable. This was noted in two cases.

SPECIAL INVESTIGATIONS

Electrocardiographic Findings

A typical electrocardiogram is shown in Figure III, taken from Case VII. As has already been mentioned, all patients remained in sinus rhythm. The *P* wave measured from 1·5 to 3·5 mm. in height, with a mean of 3·1 mm. All patients had evidence of considerable right ventricular hypertrophy, with a tall *R* wave

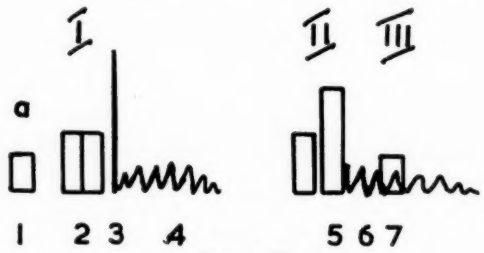

FIGURE II

The auscultatory findings in pulmonary hypertension. I, II and III refer to first, second and third heart sounds; "a" refers to right atrial sound. The incidence of these findings in this series is recorded in Table II

and inverted *T* waves in right ventricular leads, together with clockwise rotation. In extreme cases *T* wave inversion extended from *V*1 to *V*6. Five patients had a *qR* pattern in lead *V*1. (See Figure III.)

Radiological Findings

A typical X-ray picture is shown in Figure IV, from Case I. Peripheral pulmonary oligæmia was present in all cases. Cardiac enlargement involved the right atrium and the right ventricle, and was moderate only (cardio-thoracic ratio

50% in all cases). In some cases cardiac dilatation increased before death. Figure V (*a* and *b*) from Case III illustrates this. However, this was not invariable, and Figure IV was taken only two months before the death of this patient. In this series the enlargement of the main pulmonary artery was moderate only. This may be due to the rapid downhill course in these cases, for in this disease the enlargement may be quite gross. The dilatation of the right pulmonary artery was never marked.

pressure. This is well shown in Figure VI, where the systemic pressure was 100/65 and the pulmonary artery pressure 150/80 mm. Hg at the time when the record was taken. In all cases the cardiac output was low and the pulmonary vascular resistance was greatly raised. The highest output and lowest resistance were found in Case IV; this patient was the girl, aged 10 years, who was symptom-free. In Case III on exercise, the pulmonary artery pressure was unchanged, but the cardiac output dropped to 1·9 litres per minute, and the

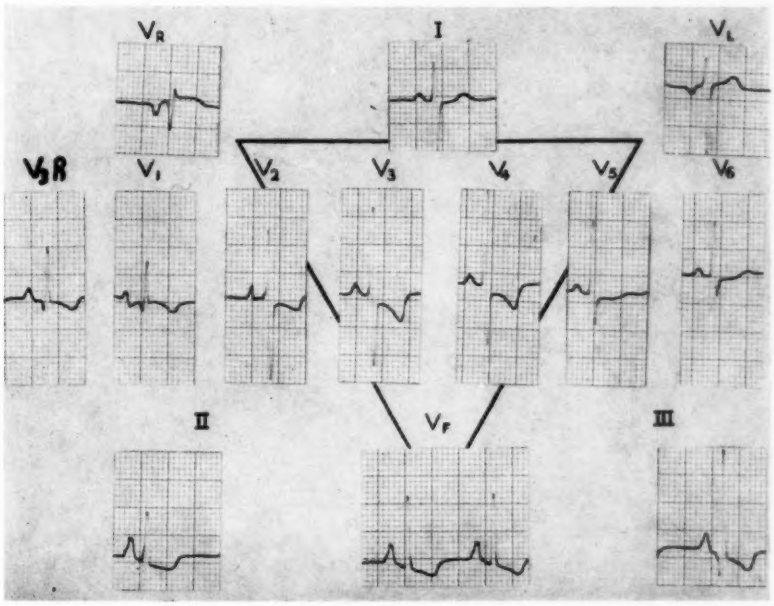

FIGURE III

Electrocardiogram, Case VII, showing 3·5 mm. *P* waves and right ventricular strain pattern with clock-wise rotation. There is a *qR* pattern in lead *V*1.

Cardiac Catheterization

In all these cases the clinical diagnosis was made before cardiac catheterization. This was carried out in all cases—in Cases I and II at the Royal North Shore Hospital of Sydney, and in the remainder at the Hallstrom Institute of Cardiology. The relevant data are presented in Table III. In none of them was there any arrhythmia or any cause for alarm during or after the procedure.

Intracardiac defects were always carefully sought, but never found.

In five cases the pulmonary artery systolic pressure was 100 mm. Hg or over. In three it equalled or exceeded the systemic arterial pulmonary vascular resistance rose to 32 units. In Case V on exercise, the pulmonary artery pressure rose to 170/85 mm. Hg and the cardiac output fell to 2 litres per minute, pulmonary vascular resistance being over 45 units.

Wedge pulmonary artery pressures may be difficult or impossible to obtain in pulmonary hypertension. In two of these cases this was so; but in the remaining six satisfactory traces were obtained and the pressures were normal.

In all cases careful sampling of the right side of the heart revealed no left-to-right shunt.

The arterial saturation was below 90% in five cases. The mean figure was 87·5%. It is likely that many of these figures were

lower before death. The lowest figure (80·4%) was recorded two months before death, and the highest (94%) in the symptom-free child.

The hæmoglobin value ranged from 13·7 grammes per 100 ml. in the child to 20·6 grammes per 100 ml. in her mother. The level was over 18 grammes per 100 ml. in all but Case IV, and averaged 18·6 grammes per 100 ml.

Dye injections into the right side of the heart with sampling from the brachial artery were carried out in five cases. In three of these no

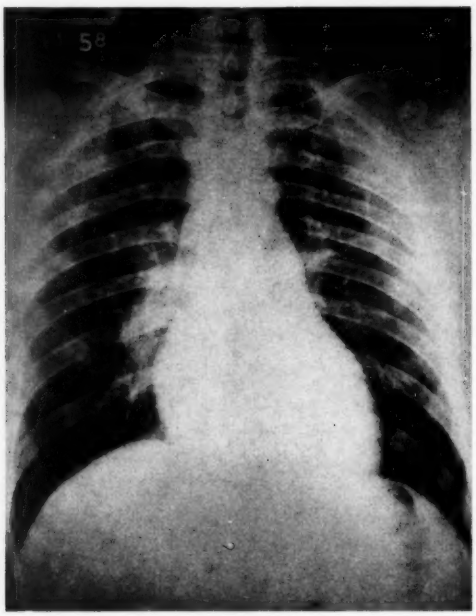

FIGURE IV

Postero-anterior radiograph, Case I, showing peripheral pulmonary oligæmia and moderate enlargement of the right side of the heart and the pulmonary trunk

right-to-left shunt was demonstrated. In the other two, evidence of a right-to-left shunt was obtained. In Case VII this was clearly localized to the right atrium. Figure VII shows curves obtained by injection into the superior vena cava and the main pulmonary artery. The superior vena cava curve shows an early peak indicating a shunt at atrial level, presumably through a patent foramen ovale. The curve from the main pulmonary artery shows no such early peak. The curve from the superior vena cava is also flatter and more prolonged than that from the pulmonary artery. This is due to tricuspid incompetence (Korner and Shillingford, 1955).

Effect of Measures Designed to Lower the Pulmonary Artery Pressure and the Pulmonary Vascular Resistance.—Various measures have been reported as having an effect on the tone of the pulmonary vasculature in pulmonary hypertension. The results obtained by a trial of these measures are shown in Table III.

Acetyl choline, 1·0 to 1·5 mg., as the most potent agent, was used initially. In the four cases in which it was tried, it was effective only in that of the girl aged 10 years, in whom it caused a 10 mm. drop in the pulmonary artery systolic pressure. In no other case was there any effect. "Serpasil" (1 mg.) showed no effect in the two cases in which the cardiac output and pulmonary artery pressure were measured at intervals up to an hour after injection. Oxygen (100%) was used in four cases, but lowered the pulmonary artery pressure in the girl only. The lowering was again by 10 mm. (systolic).

Pulmonary Function Tests.—In this series, pulmonary function tests were carried out in five of the cases. The ventilatory function was normal. This was striking, even in severely incapacitated patients. Hyperventilation at rest was common. This was reduced by breathing 100% oxygen, which suggested that there was an anoxic stimulus to respiration. In the two cases in which it was estimated, the carbon dioxide tension was low (20 and 28·3 mm.). The carbon monoxide diffusion capacity tended to be low. The mean normal figure for this laboratory is 16 ml. per millimetre of mercury. In the five cases studied it ranged from 7 to 20, with a mean of 12. It is unlikely that it could be much increased on exercise. These findings are consistent with reduction in the capacity of the pulmonary vascular bed and the low cardiac output.

SUBSEQUENT COURSE

The subsequent course is set out in Table I. In all cases, from the time of appearance of symptoms there is a steady deterioration.

In this series four patients are known to have died. One cannot now be traced, and it is almost certain that she must have died. All but one of these had died within 18 months after the appearance of symptoms. Four of these were very active people, fond of vigorous sport before their symptoms appeared. In Case VII the patient is deteriorating rapidly. The patient in Case II is deteriorating very slowly, but needs treatment for congestive cardiac failure.

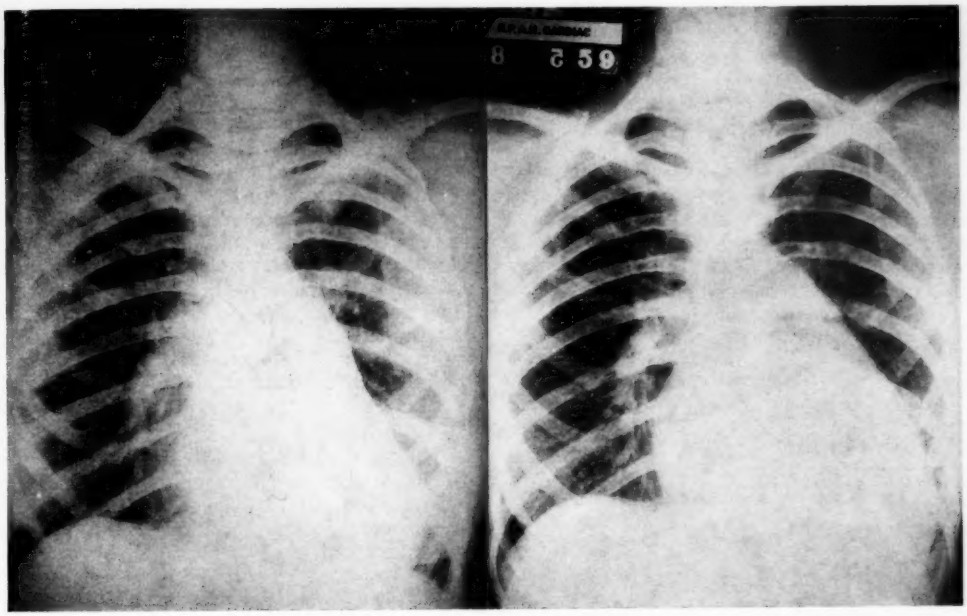

FIGURE V

Case III. Postero-anterior radiographs, taken (on left) six months before death and (on right) one month before death, showing considerable terminal cardiac dilatation

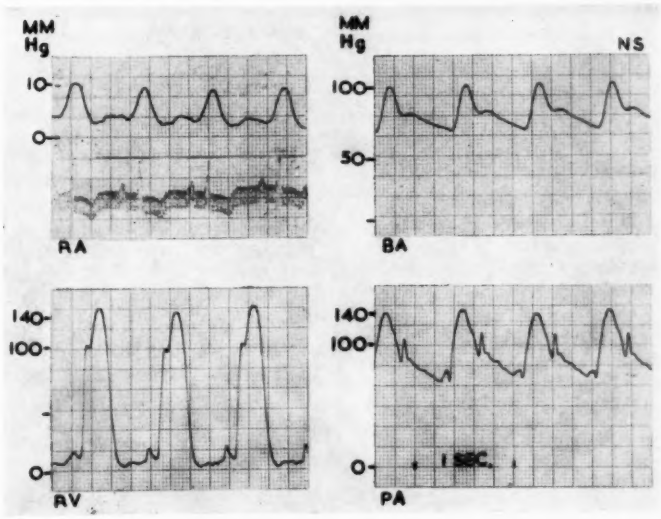

FIGURE VI

Pressure pulse tracings recorded at catheterization in Case V, paper speed 25 mm. per second. The pulmonary artery (P.A.) systolic pressure exceeds the brachial (B.A.) by 50 mm. Hg. The right atrial (R.A.) giant *a* wave is well transmitted to the right ventricle (R.V.) and the pulmonary artery (P.A.)

The patient in Case IV, aged 10 years, is symptom-free.

In all cases death has ended a distressing state of low cardiac output with terminal congestive cardiac failure. In Case V the patient developed a retinal vein thrombosis in spite of anticoagulants.

Sudden death due to ventricular arrhythmia is common, but did not occur in this group of patients.

One has become accustomed to regarding this diagnosis as having a more malignant prognosis than carcinoma of the lung.

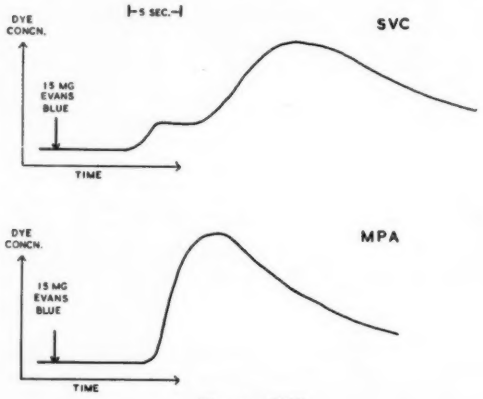

FIGURE VII

Dye dilution curves recorded from the brachial artery in Case VII. The curve from injection into the superior vena cava (S.V.C.) shows an early peak due to right-to-left shunting and flattening of the curve from tricuspid incompetence. The curve from injection into the pulmonary trunk (M.P.A.) is of nearly normal appearance

FAMILY INCIDENCE

The incidence of primary pulmonary hypertension in the family of patients M.S. (1) and L.S. (2) is shown in Figure VIII. (The numbers 1 to 4 on this figure do not correspond to those in Table I.)

Patient 3 in Figure VIII, who was a step-sister of M.S., is not included in the present series. She was investigated at the Alfred Hospital, Melbourne, and the diagnosis of pulmonary hypertension was confirmed. She is survived by her entire family of two sons and one daughter (personally examined), who are all healthy and range in age from 22 to 25 years. Her mother died at the age of 32 years from pneumonia.

The mother of M.S. is still alive and well. Two of her (the mother's) brothers died suddenly at the ages of 54 and 60 years, but no details of the diagnoses are available.

Patient 4 in Figure VIII was a cousin of patient M.S. (1). His mother is alive and well, and his father died of carcinoma. The patient himself died suddenly at the age of 30 years. A year previously he had been rejected for employment because he was under weight and of poor physique. Physical examination then revealed no other abnormalities. I have examined an X-ray film taken at that time, and it shows oligæmic lung fields and considerable enlargement of both the right atrium and the right ventricle. The pulmonary artery was not particularly enlarged. Shortly before he died he suffered from several attacks of syncope on exertion. He died after a syncopal attack. It is possible that he suffered from pulmonary hypertension, though there can be no proof of this.

In spite of much correspondence, it has not been possible to fill in more details in this family tree. Members of this family are now widely scattered, and their doctors have frequently left the districts in which they lived. No other subjects who could be suspected as suffering from pulmonary hypertension have been detected. There is no known relationship between the successive wives of the father of Patients 1 and 3.

There are thus the step-sister and the daughter of patient M.S. proved to suffer from pulmonary hypertension, and a male first cousin possibly dying from it. It is difficult to see any particular hereditary trait that would cause this distribution. However, the incidence in this family is too great to occur by chance, and it is likely that some factor is present in the family of the father of Patients 1 and 3. All these patients were born and spent their youth in Lake Cargelligo (altitude 555 feet above sea-level) in western New South Wales. Bilharzia or any other known cause of pulmonary hypertension is not recognized in this area. The habitat of all eight patients in this series is recorded in Table I. It will be seen that it covers many thousands of square miles.

PATHOLOGICAL FINDINGS

Detailed pathological studies have been reported by Wade and Ball (1957), by Shepherd *et alii* (1957), by Evans *et alii* (1957) and by Heath *et alii* (1959). The subject is particularly well reviewed by Whitaker and Heath (1959).

In the present series, only one subject has come to autopsy (Case I). This regrettable lack of necropsy data is largely due to the great distances involved. The findings in this case were in all respects similar to those reported elsewhere. It was notable that there was no valve, patent foramen ovale or any other intracardiac defect. This will be discussed later. Examination of sections from the pulmonary artery trunk showed the elastic tissue to be characteristic of acquired rather than congenital pulmonary hypertension (Heath *et alii*, 1959). This is indicated by the branching, fragmentation and clubbing of the fibres. Dr. Heath (personal communication) has been

kind enough to check this finding. He and Edwards (Heath and Edwards, unpublished data) have now histologically examined the pulmonary trunk of six subjects with this diagnosis proven. In five of them the appearance was of the acquired type, while in the only male in the group the appearances were of the congenital type.

In the muscular arteries, medial hypertrophy is the rule. Intimal changes and localized dilatations are frequent, but these lesions may be quite focal and must be looked for with great care. Vascular obstruction with bronchofails to look at the jugular venous pressure. Three of these patients had been investigated by barium X-ray studies because of this pain and the weight loss. Hoarseness of the voice due to recurrent laryngeal nerve palsy did not occur in this series. This has been reported (Brinton, 1950) as being due to the gross enlargement of the main pulmonary artery. Its absence in this series is perhaps due to the fact that in no case was there extreme dilatation of the pulmonary artery, probably owing to the rapid course. Only in Case VI did the patient suffer chest infections.

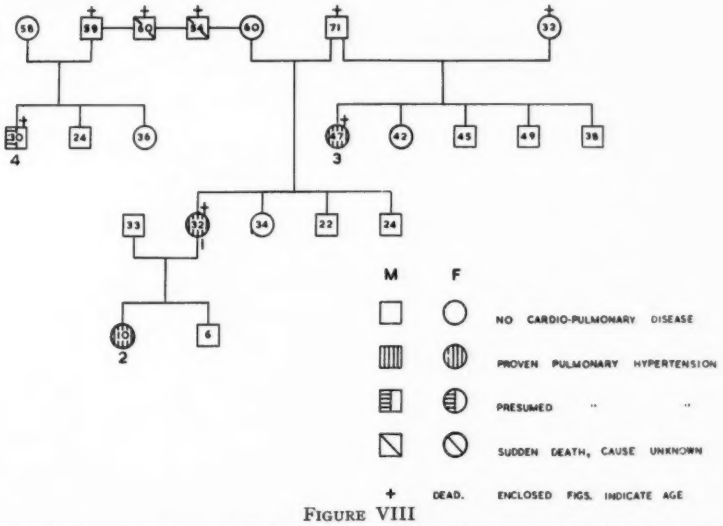

FIGURE VIII

The family tree of patients M.S. and L.S. The numbers below the circles are for reference, in the text, to patients. They do not correspond to the numbers used in Tables I and III. Patient M.S. is (1) in this figure and L.S. is (2)

pulmonary anastomoses has been demonstrated (Wade and Ball, 1957; Evans *et alii*, 1957; Short, 1957). As Whitacker and Heath (1959) indicate, these changes are in no way specific and will occur in any acquired pulmonary hypertension of severe degree. Necrotizing arteritis and pulmonary thrombi and emboli may also be found.

DISCUSSION

The clinical picture is clear. In the classical case the patient is a young woman who has previously been active and in good health. She notices dyspnœa on exertion, fatigue, syncope and possibly angina. Sensitivity to cold, the pain of hepatic congestion and weight loss are frequently added. The pain of hepatic congestion, as in other forms of heart disease, is frequently not recognized by the doctor, who

The onset is insidious, and the correct diagnosis is often made late. Patients may be incorrectly considered to be neurotic or suffering from abdominal disorder. The signs are those of pulmonary hypertension with a low cardiac output. These are quite characteristic, but are frequently overlooked. Deterioration may be rapid, with death in congestive cardiac failure or due to sudden ventricular arrhythmia. The downhill course is so relentless as to merit the term malignant.

Wood (1956) found the average duration to be 3·2 years, with a range of from one month to 10 years. Evans *et alii* (1957) record deaths occurring at ages varying from seven to 64 years.

Cardiac catheterization was uneventful in the eight cases reported. Catheterization and other minor procedures have been reported as

causing sudden death in these patients (Wade and Ball, 1957; Chapmen *et alii*, 1957). A particularly alarming report comes from Schafer *et alii* (1956), who record three such deaths following completion of catheterization. In all these cases the pulmonary systolic pressure was over 150 mm. Hg. There is undoubtedly increased risk in advanced cases. In all patients the pulmonary artery pressure was greatly raised, the cardiac output was low, and the pulmonary vascular resistance was very high. No intracardiac defects were found by catheter search, blood sampling or dye-dilution curves.

Differential Diagnosis

The differential diagnosis is considered in detail in the reports already referred to. Hitherto, the difficulties have perhaps been overestimated (Brachfield *et alii*, 1958), and in practice the picture tends to be so characteristic that there is little doubt about the clinical diagnosis. The full differential diagnosis will not be considered here, but it is important to make an accurate diagnosis so that treatable conditions will not be overlooked. This will also enable an accurate prognosis to be made.

Mitral stenosis must be first excluded, for when there is extreme elevation of the pulmonary vascular resistance the signs of stenosis may be completely masked. However, a clue is usually given by a rheumatic history, a loud mitral first sound, dilatation of the left atrium, calcium in the valve or a *P* mitrale on the electrocardiogram. If a wedged pulmonary artery trace is not obtainable, it is reasonable to record the left atrial pressure pulse by transbronchial puncture.

It is also important to recognize thromboembolic pulmonary hypertension, which can well be treated by anticoagulants. This occurs particularly in puerperal young women and in young men, often after relatively minor trauma. Early recognition and treatment may restore the circulation to normal. Untreated, this is an incapacitating and frequently fatal disorder. Although four of the six women in this series had children, there was nothing abnormal about the pregnancy or puerperium, and neither in these patients nor in the men was there anything to suggest an embolic episode. At necropsy in Case I this was confirmed.

Diffuse collagen disorders should be excluded, as treatment with steroids may be helpful (Wade and Ball, 1957).

The Eisenmenger syndrome can usually be identified on clinical grounds (Wood, 1958*a*). This may be confirmed by catheterization. The prognosis is rather better than in primary pulmonary hypertension, as there is an alternative route of outflow from the right side of the heart. This is an important reason for establishing the diagnosis.

The Effect of Measures Designed to Lower the Pulmonary Vascular Resistance.—There is good evidence (Daly, 1956; Gorlin *et alii*, 1958; Cournand, 1957; Shepherd, 1958) that the pulmonary vasculature may be under nervous control. Various substances have been reported as lowering a raised pulmonary vascular resistance. Among these are acetylcholine (Wood, 1956); Wood also records success with "Priscol" and aminophyllin. "Priscol" has been described as being effective by Dresdale *et alii* (1954), by Wade and Ball (1957) and by Rudolph *et alii* (1958); ganglion-blocking agents have been found useful by Wade and Ball (1957), and 100% oxygen has been found satisfactory by Shepherd *et alii* (1957) and "Serpasil" by Halmagyi *et alii* (1957). Of these, acetylcholine is convenient to use first, as it appears to be the most potent agent. Its action is immediate and transient, and the effect is usually obtained with 1·0 mg. or not at all. Wood (1958*b*, 1958*c*) reports success with this drug in five out of the six cases in which it was tried. Two of these patients had been known to suffer from the condition for four and eight years respectively. In the present series, this effect could be shown only in the girl, aged 10 years, who was symptom-free. Wood has suggested that the good response to acetylcholine in his cases is evidence for the acquired nature of the disorder.

Treatment

Because of the unknown ætiology of this disorder, no fundamental treatment is possible. The use of the drugs demonstrated to lower the pulmonary vascular resistance under catheter conditions has shown no convincing benefit. The patient in Case IV is being maintained on "Serpasil", on the chance that it may be beneficial. Treatment is directed at the congestive failure and thrombo-embolic phenomena. Prednisone has been used in this series with no apparent benefit. There are few more therapeutically hopeless situations remaining in medicine.

Polycythæmia

Polycythæmia is commonly attributed to tissue anoxia, but it must also be related to the arterial desaturation which was frequent in this series. Shepherd *et alii* (1957) have attributed this to opening of a valve patent foramen ovale. While this may have been so

in Cases VI and VII, in which dye studies indicated a shunt at atrial level, it was not so in Case I, in which no intracardiac communication was found at autopsy. Evans *et alii* (1957) have also noted this, and have found patent foramen ovale present in only two of their 11 autopsy cases. They join Wade and Ball (1957) in suggesting that it may be due to shunting through the enlarged broncho-pulmonary anastomoses which they had demonstrated. Evans *et alii* (1957) record one case in which the arterial saturation was as low as 63%.

Pulmonary Function

Few studies of pulmonary function have been made in this condition. McIlroy and Apthorp (1958) include four cases in their series of pulmonary hypertension of various ætiologies. Measurements of lung mechanics and the diffusion of carbon monoxide were measured in only one case of primary pulmonary hypertension.

The arterial desaturation and the polycythæmia cannot be related to defect of pulmonary function. The ventilatory function is normal. Hyperventilation at rest is common, and the arterial carbon dioxide tension may be low. The carbon monoxide diffusing capacity is in the lower range of normal. It is suggested that these findings are compatible with reduction in the capacity of the pulmonary vascular bed and low cardiac output.

Ætiology

The pathogenesis of this disorder is still under dispute. In the meantime it seems reasonable to regard it as an increase in the tone of the pulmonary arterioles, to which are soon added irreversible organic changes. The increasing number of cases being reported with a familial incidence may provide a clue to the basis of this disorder. The family reported in this study shows no clear genetic trend. A factor common to the cases in this family would appear to be a geographical one in early life. However, this has had no known effect on other people in the same area.

While this paper was in preparation, Coleman *et alii* (1959) published an excellent report of a brother and two sisters who died of primary pulmonary hypertension. This was confirmed in each case by detailed necropsy studies. Other members of the family may have suffered from the same disorder. They suggest that the disease may have a congenital basis, and they find support for this in the number of congenital defects that have occurred in other members of the same family.

The ætiology of this condition must be regarded as quite unknown. The evidence of the elastic fibres in the pulmonary trunk and the response of some patients to acetylcholine would suggest that it is an acquired disorder. Early cases have not yet been detected. Even Case X, which was picked up through the patient's mother, must be regarded as a well-established case. Reports such as this, of a familial incidence of the disorder, would suggest that congenital factors are not unimportant. It is possible that there may be a congenital predisposition to the disorder.

ACKNOWLEDGEMENTS

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CLINICO–PATHOLOGICAL FEATURES OF ACUTE HÆMORRHAGIC LEUCOENCEPHALITIS[1]

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SUMMARY

Three cases of acute hæmorrhagic leucoencephalitis are described; the patients were admitted to the one hospital over a period of three months. All cases were associated with an acute respiratory illness.

As these cases presented a definite clinical syndrome, with headache, scattered cerebral signs and sterile cerebro-spinal fluid containing polymorphs, it is our view that in future cases, once cerebral abscess has been excluded, it may well be possible to establish a diagnosis during life and to institute therapy.

SINCE Hurst (1941) described two cases of an acute cerebral condition, which he termed acute hæmorrhagic leuco-encephalitis, several further cases have been described. This disease usually has an abrupt onset following an acute upper respiratory tract infection, and is generally fatal in from one to six days. It occurs more often in men than in women, and most of the patients are young adults. The clinical manifestations vary and depend on the location of the primary damage to the brain. There is frequently gross asymmetry of the signs, with early onset of confusion and coma. The diagnosis has usually been made at autopsy, when the findings have been zones of demyelination, hæmorrhages, cellular infiltration and œdema, mainly in the white matter of the cerebrum.

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Because the disease is rare and difficult to diagnose clinically, we are describing three cases. The patients were admitted to the Royal Prince Alfred Hospital within three months, and presented rather typical clinical histories, autopsy findings and histopathological changes (Table I).

CASE I

Clinical Record

A man, aged 28 years, was admitted to hospital early in the morning of October 31, 1958. He had had bronchitis for two weeks, but had been otherwise well until midday of October 30, when his left arm became paralysed. Later in the day he lost the use of his left leg and complained of a dull frontal headache. This was followed by vomiting and three convulsions, which led to his admission to hospital. He was then very apprehensive, and shortly afterwards had a tonic-clonic convulsion commencing in the fingers of the left hand and passing to the shoulder, mouth, trunk and left leg. When he was examined after this, there was increased tone in the left limbs with absence of any movements in them. The right pupil became dilated and unreactive to light. Rhonchi were heard in the left lung, and his temperature was 99·4° F. Lumbar

TABLE I

Summary of Main Feature

Case Number	Patients Age (Years)	Sex	Associated Respiratory Infection	Symptoms and Signs	Duration	Cells in Cerebro-Spinal Fluid (per Cubic Millimetre)	Morbid Anatomy
I	28	M.	Bronchitis for two weeks	Left hemiplegia; convulsions	46 hours	2800 leucocytes	Multiple hæmorrhages and patchy demyelination, principally in white matter of right hemisphere
II	32	M.	Chronic bronchitis	Severe headaches; confusion; right hemiparesis	18 days	16 leucocytes 7660 red blood cells	Multiple bilateral hæmorrhagic softening of white matter only
III	28	M.	Bronchitis found at autopsy	Headache; left hemiplegia; coma	5 days	735 leucocytes	Multiple bilateral minute softenings and some hæmorrhages in white matter only

puncture yielded turbid cerebro-spinal fluid at a pressure of 150 mm. of water, which contained 2800 white cells per cubic millimetre, all of which were polymorphs. The protein content was elevated to 200 mg. per 100 ml., and the chloride content was 690 mg. per 100 ml. Gram staining revealed no organisms.

FIGURE I

Case I: multiple hæmorrhages and softening in the white matter. (Actual size)

FIGURE II

Case I: polymorphs in the perivascular sheath of a vessel and a ring hæmorrhage in the left corner. (Hæmatoxylin and eosin stain. ×150)

The presence of a right-sided cerebral abscess with meningitis was suspected, and was not excluded by a right carotid angiogram, which showed a displacement of the major blood vessels, suggesting swelling of the right frontal and anterior parietal regions, or a space-occupying lesion. Exploration of the brain by needling through frontal and parietal burr-holes revealed extensive softening without any abscess formation. The patient's condition continued to deteriorate steadily, and he succumbed on November 1, about 46 hours after the onset of his acute symptoms.

Post-Mortem Findings

The lungs and brain only were abnormal. Small bilateral pleural effusions were present. The bronchi of both lungs contained thick mucopurulent secretion, and the mucosa was reddened and velvety. Patchy areas of pneumonic consolidation were seen throughout the lungs, particularly in the lower lobes.

There was some herniation of the brain through the recent burr-holes in the right and left frontal and right parietal regions. Slight cerebellar coning and flattening of the cerebral gyri were seen on removal of the brain, which weighed 1680 grammes. The vessels over the brain surface were congested. The right parietal lobe was swollen and soft, with patchy opacity of the meninges in this region. The brain was sectioned horizontally at the level of the roof of the lateral ventricles. Numerous minute hæmorrhages were present throughout the white matter of the right cerebral hemisphere, but did not extend into the cortex (Figure I). The hæmorrhages were more concentrated in the parietal lobe, although the frontal and occipital lobes were also affected. The white matter was quite soft, particularly where the hæmorrhages were most numerous. The right cerebral peduncle at the level of the pons showed severe hæmorrhagic softening. The left cerebral hemisphere did not appear to be affected.

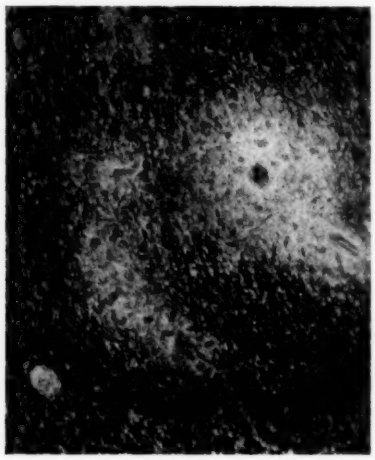

FIGURE III

Case I: perivascular demyelination. (Weil's myelin stain. ×75)

Histopathological Findings

Throughout the white matter of the right cerebral hemisphere were multiple small hæmorrhages, of both ball and ring types, extending into the cortex in some areas. The perivascular sheaths, particularly in the white matter, but to some extent in the grey matter, showed polymorphonuclear infiltration (Figure II). There was also diffuse infiltration with polymorphs in the right cerebral hemisphere and in the meninges

of the cerebrum and cerebellum on the right side. Many of the walls of the small vessels were necrotic. Quite large portions of the white matter of the right hemisphere showed œdema and stained irregularly and faintly, and myelin stains showed extensive demyelination, which was often perivascular (Figure III). Sections of the left side showed no polymorphonuclear infiltration and only slight vascular congestion.

CASE II

Clinical Record

The patient, a storeman, aged 32 years, had been living in Australia for nine years. He had a long history of coughs and colds and morning sputum, of five years' duration. Two weeks before his admission to hospital on September 26, 1958, he suffered from persistent and severe headache over the left eye, and he had been vomiting for four days. On his admission he was agitated, but without any definite abnormality in the central nervous system. Examination of the cerebro-spinal fluid showed no significant increase in white cells, and a slight elevation of protein content to 90 mg. per 100 ml. An electroencephalogram showed a 9 to 10 c.p.s. alpha rhythm, which blocked normally on visual attention. In the left temporal area high-voltage 3 to 4 delta waves were noted. These changes suggested a space-occupying lesion in the left temporal lobe.

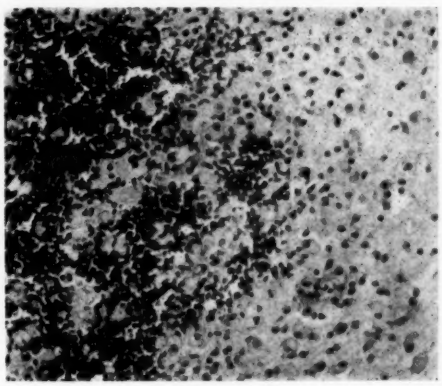

FIGURE IV

Case II: hæmorrhage and compound granular corpuscles replacing the white matter. (Hæmatoxylin and eosin stain. ×150)

On September 29, he became confused and incontinent of urine and fæces, and developed spastic paresis of the right arm and leg. Left cerebral angiography confirmed the electroencephalographic findings, and a left temporal burr-hole was made. Yellow necrotic material was aspirated from the temporal lobe, but histological examination showed only "amorphous, acellular débris". He then became deeply comatose, and died on the following day, four days after his admission to hospital. Examination of a smear of his sputum showed profuse pus cells and a mixed growth, with pneumonocci predominant.

Post-Mortem Findings

The lungs were found to be congested, but showed no other evidence of inflammation. A few small erosions were found in the gastric mucosa.

The brain weighed 1500 grammes and it was œdematous, the left parietal region being softer than the right. The cerebellar tonsils had herniated through the foramen magnum. Needle tracks were seen in the left cerebral hemisphere, and some blood clot was found in the aqueduct and in the fourth ventricle, as well as around the needle tracks. In the white matter of both cerebral hemispheres there were mottled areas of softening and small hæmorrhagic spots. These spots were also present throughout the pons.

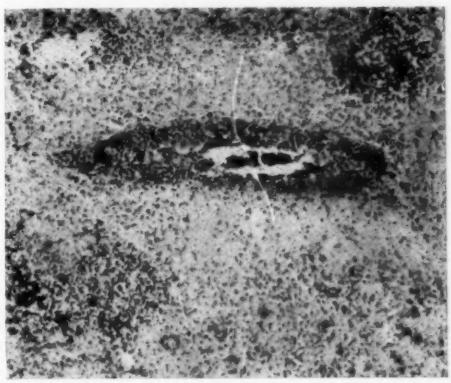

FIGURE V

Case II: portions of the wall of the vein in the centre show hyaline necrosis. There is perivascular cuffing with polymorphs, and polymorphonuclear infiltration and softening of the white matter. (Hæmatoxylin and eosin stain. ×75)

Histopathological Findings

The brain lesions were found to be situated mainly in the basal ganglia and in the surrounding white matter on both sides. Throughout the affected areas were many irregular zones of demyelination, in which the white matter was largely replaced by compound granular corpuscles and erythrocytes (Figure IV). Vessels running through these parts showed hyaline necrosis of their walls, but were not occluded by thrombi. Adjacent white matter showed prominent gemistocytic astrocytes and perivascular cuffing, with polymorphs (Figure V). The appearances were those of multiple small scattered softenings, at times confluent.

CASE III

Clinical Record

On November 30, 1958, a man, aged 28 years, presented himself at Goulburn Base Hospital with a history of intense bitemporal headache, which had commenced suddenly 12 hours before. He had previously been quite well. The cerebro-spinal fluid was under normal pressure and contained 735 cells per cubic millimetre, most of which were round cells with a few polymorphs. That evening he became drowsy and developed spastic paralysis of the left leg and arm, the left plantar response being extensor. His temperature was 101·4° F., and a blood count showed a leucocytosis of 19,900 cells per cubic millimetre, 84% being neutrophils. When he was transferred to Royal Prince Alfred Hospital on December 3, he was in a coma and had neck stiffness. There was right third nerve and left facial paresis. The right elbow was

spastic and the wrist joint was flaccid, both lower limbs showing flaccid paresis. A diagnosis of cerebral abscess was made. The cerebro-spinal fluid, which looked normal, contained 25 mg. of protein per 100 ml. and 720 mg. of chloride per 100 ml., and no organisms were seen in a smear. He regained consciousness,

FIGURE VI

Case III: scattered zones of demyelination in the white matter with normal grey matter on the left. (Weil's myelin stain. ×10)

but was not cooperative. On December 4, 1958, right carotid angiography showed a slight shift of the anterior cerebral arteries to the left, but the findings were otherwise normal. An electroencephalogram showed a marked hemisphere asymmetry. On the left side there was 10 to 11 c.p.s. alpha rhythm. In both frontal areas there were 3 to 5 c.p.s. waves at

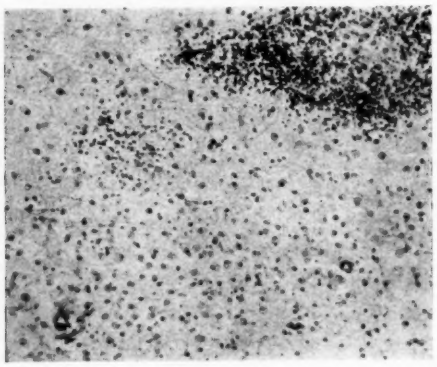

FIGURE VII

Case III: compound granular corpuscles and hæmorrhage in white matter. (Hæmatoxylin and eosin stain. ×150)

times. In the right temporal area high-voltage 2 to 3 c.p.s. delta waves were present, with phase reversals in the mid-temporal area. There were thus a distinct hemisphere asymmetry and a gross right temporal lesion, consistent with a mid-temporal abscess or possibly glioblastoma. He died on December 4, five days after the onset of symptoms.

Post-Mortem Findings

All bronchi contained pus, and there was partial collapse of the lower lobe of the right lung at the base. Some acute erosions were found in the stomach.

The brain weighed 1595 grammes. The cerebral hemispheres were enlarged and the sulci flattened, and there was herniation of the uncal gyri through the tentorium. The outer surface of the brain was pink and congested. On the cut surface minute hæmorrhages caused a stippled effect throughout both cerebral hemispheres, and the white matter on the right side had a yellowish colour. The grey matter and the cerebellum did not appear to be involved, and the vessels at the base of the brain were normal.

Histopathological Findings

In the brain there were many small scattered zones of demyelination of the white matter (Figure VI). In these zones there were collections of closely-packed compound granular corpuscles, and groups of red blood cells (Figure VII). In some places hæmorrhage had occurred around small vessels, but no eosinophilic necrosis was seen. The changes ended abruptly at the grey matter, which appeared quite normal.

DISCUSSION

The three cases of acute hæmorrhagic leuco-encephalitis we have described conform to the pattern described by Weston Hurst and most subsequent writers. All three occurred in young men. One was recovering from an attack of acute bronchitis, another had a long history of chronic bronchitis, while the third was found to have bronchitis *post mortem*. Severe headache was an early symptom in all, with the neurological developments varying according to the part of the brain most affected. In the first case the left-sided hemiplegia was followed by signs of swelling of the brain. Convulsion and coma followed, and the patient died within two days. In this case, as in the other two, cerebral abscess was thought the most likely diagnosis. The second patient had severe headaches for two weeks before developing incontinence of urine and fæces and spastic paresis of the right arm and leg and, finally, confusion, coma and death. The third patient had a 24-hours' history of severe bitemporal headache before he became drowsy and developed a spastic paralysis of the left leg and arm. Further neurological signs were recorded before he died.

The course in two cases was rapid ,and in the other a rapid final illness was preceded by headache for two weeks. This, too, conforms with a case previously described, for although the disease is generally fatal within five to six days, Southcott and Fowler (1954) described a case in which the patient survived for 18 days.

All three patients were febrile at some time, and two had leucocytosis; in Case I the blood count was not recorded. In two cases the

cerebro-spinal fluid contained many leucocytes, but was sterile.

The findings in the brain at autopsy also resembled those previously described. The lesions were patchy and hæmorrhagic, and demyelination of the white matter was a feature. The polymorphonuclear invasion of the meninges and perivascular spaces was also striking.

It appears, therefore, that this is a definite disease entity, with a typical clinical course. While no feature is in itself diagnostic, there is a similarity of overall pattern which suggests that the disease may be diagnosed during life. The polymorphonuclear response in the cerebro-spinal fluid in the absence of organisms, with signs of scattered cerebral damage, should suggest this as a possible diagnostic alternative to cerebral abscess.

The ætiology of this condition is unknown. Adams *et alii* (1949) described four cases of "acute necrotizing hæmorrhagic encephalopathy", which many other authors have classified with acute hæmorrhagic leuco-encephalitis. They were unable to transmit the disease to mice by intracerebral inoculation of emulsified brain from one of their patients, and they concluded that "the possibility of an allergic reaction to a toxin or infective agent seems most consistent with the pathological findings". Other workers (Southcott and Fowler, 1954) have failed to culture a virus from the central nervous system, and have also failed to transmit the disease experimentally to monkeys by inoculation of emulsified brain.

A review of the literature reveals that of the cases reported, some apparently occurred in groups. Adams *et alii* (1949) reported three cases at Boston between August and October, 1946, and Crawford (1954) described two cases from St. George Hospital, London, occurring within six months. The present three cases occurred between September and November, 1958. While this could imply increased awareness amongst observers, it also suggests that there may be some epidemiological significance.

In cases of acute brain disturbance with fever, it is the clinician's first responsibility to identify or exclude lesions amenable to surgery or antibiotics; this may require cerebral angiography and exploration of the brain by needling. Acute hæmorrhagic leuco-encephalitis may be diagnosed in this way, and possibly treated as an allergic reaction with corticosteroids.

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OBSERVATIONS ON THE TREATMENT OF SEVERE DIABETIC KETOSIS[1, 2]

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SUMMARY

A series of 32 patients with severe diabetic ketosis treated by us during 1956–1957 has been compared with a similar group of 67 patients admitted to the Alfred Hospital, Melbourne, between 1952 and 1955.

This comparison has shown that the mortality has decreased during 1956–1957. The reasons for this have been analysed and discussed, and the rationale for the present régime of treatment is presented.

It is concluded that the reduction in mortality has been due to several factors, which include the following: (i) the management of diabetic ketosis by one unit; (ii) the use of alkaline solutions at the commencement of treatment; (iii) the administration of potassium salts early in treatment; (iv) a reduction in the severity of the condition on the patients' admission to hospital.

The need is stressed for educating patients and practitioners in the early recognition of this disorder so that mortality may be further reduced.

TREATMENT of severe diabetic ketosis involves an appreciation of the complexities of the metabolic disorder, and of the importance of the attention to detail in management and of preventing or minimizing further ketotic episodes.

Although the clinical manifestations vary in degree, most patients show evidence of dehydration and many have laboured respirations or air hunger and, in addition, drowsiness or coma; and occasionally peripheral circulatory failure may be present.

Hyperglycæmia and ketonæmia usually result in marked electrolyte depletion with eventual acidæmia, so that it is not possible to know which disturbance is lethal in any one patient. In this disorder two of the most important factors are the severe dehydration and acidæmia that result from uncontrolled hyperglycæmia and continuing ketosis.

The results of treatment of two groups of patients will now be compared. This study has been undertaken to determine whether mortality has been influenced by differences in treatment. The two groups relate to patients admitted to the Alfred Hospital, Melbourne, during the periods 1952–1955 and 1956–1957.

In the first period (Group I), 55 patients were admitted on 67 occasions to different units in the hospital, and no uniform pattern of treatment was followed. During 1956–1957 (Group II), all patients with severe diabetic ketosis were admitted under the care of the Diabetic and Metabolic Unit. Every patient from this group was examined by one of us, and most received a uniform régime of treatment. This group comprised 32 episodes of ketosis in 28 patients. The régime of treatment was as follows:

Phase I: Correction of Dehydration and Acidosis (0 to 6 Hours)

(A) Insulin: (i) Initial dose: 100 to 200 units of crystalline insulin, of which half is given intravenously if peripheral circulation is poor. (ii) Maintenance dose: 50 to 100 units each hour until glycosuria and ketonuria (or hyperglycæmia and ketonæmia) diminish.

(B) Fluids: (i) Initial dose: M/6 sodium lactate solution, 1 or 2 litres administered in 2 or 3 hours; second litre to contain 30 to 50 mEq/l. of K°. (ii) Maintenance dose: 0·85% sodium chloride solution or 2·5% dextrose with 0·45% sodium chloride solution, with added potassium (20 to 30 mEq/l.). (iii) Total fluids: between 2 and 3 litres for the average adult within 6 hours.

(C) Other measures: (i) Appropriate antibiotic treatment for infection. (ii) Gastric aspiration for continued vomiting.

Phase II: Restoration of Cellular Losses (6 to 24 hours)

Insulin: Crystalline insulin 2 to 4 hourly according to needs, as shown by blood or urinary sugar estimations.

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Fluids: 5% dextrose or dextrose-saline solution until adequate hydration is obtained, and the patient can take fluids by mouth with certainty.

Potassium: Continued at the rate of at least 25 mEq/l. of fluid by the intravenous route until oral intake is satisfactory.

Oral intake: Fruit juices and other liquid nourishment withheld until nausea and vomiting have ceased.

MATERIALS AND METHODS

Definition of Severe Diabetic Ketosis

The severity of ketosis in a diabetic patient has been assessed by bedside observation of the degree of dehydration, the state of the peripheral circulation, the level of consciousness and the clinical signs of acidæmia, usually supplemented by the results of biochemical determinations.

Although some authorities emphasize the importance of the plasma level of bicarbonate, in our opinion this is not reliable as the sole index of severity. Accordingly, all patients admitted to the Alfred Hospital over the six-year period 1952 to 1957 have been included if, while manifesting the clinical features of diabetic ketosis, they were shocked or unconscious or had a plasma bicarbonate level of 9 mEq/l. or less and showed ketonæmia or ketonuria.

Analysis of Material

Information about the patients admitted to hospital during 1952–1955 (Group I) has been obtained from case histories. The age, state of consciousness, and levels of blood pressure, blood sugar and plasma bicarbonate have been analysed, but it has been possible to draw only limited conclusions about the precise details of treatment and the presence of complications such as hypokalæmia and hypoglycæmia.

Most patients have been treated in accordance with the principles laid down earlier in tabular form, and have been closely followed by bedside observation. That is, their general condition, state of hydration, levels of consciousness and blood pressure and the pulse rates and urinary excretion have been closely observed, usually at half-hourly intervals.

In both groups these clinical observations have been supported by the facilities of a 24-hour biochemical service, which have included estimations of plasma sodium, potassium, chloride, bicarbonate, protein and ketone levels, blood sugar and urea estimations, and hæmatocrit. These analyses have been performed at the time of admission to hospital, and have usually been repeated at least twice in the subsequent 24 hours.

Deaths

Deaths have been classified as resulting either directly from ketosis or from some other cause ("coma" and "non-coma" deaths respectively). Death has been designated as "non-coma" only if the patient died at least 48 hours after making a clinical and biochemical recovery from ketosis and autopsy revealed unequivocal evidence of another fatal condition.

RESULTS

Among the 67 admissions during 1952–1955, there were 21 deaths attributable to severe diabetic ketosis, whereas in the 32 admissions during 1956–1957 one patient died. The relationship between "coma deaths" and the age, sex, conscious state, initial levels of blood pressure, plasma bicarbonate and blood sugar, and the total insulin dose over the first 24 hours of treatment are shown in Table I.

TABLE I

General Statistics of the Two Groups of Patients under Consideration

	Group I (1952–1955)		Group II (1956–1957)	
	Number of Patients	Coma Deaths	Number of Patients	Coma Deaths
Sex:				
Male	16	5	15	0
Female	51	16	17	1
Age (years):				
0 to 20	10	2	12	0
20 to 40	27	4	9	0
40 to 60	11	5	5	0
60 to 70	13	7	3	0
70 and over	6	3	3	1
State of consciousness:				
Conscious	40	2	26	1
Unconscious	27	19	6	0
Systolic blood pressure (mm. Hg):				
Above 100	45	6	26	1
Below 100	22	15	6	0
Plasma bicarbonate level (mEq/L):				
More than 4	44	12	20	1
4 or less	23	9	12	0
Blood sugar content (milligrammes per 100 ml.):				
600 or less	22	4	17	0
More than 600	45	17	15	1
Insulin dose (units in first 24 hours):				
0 to 800	36	12	24	0
800 or more	31	8	8	1

Fluids Given Intravenously

In both groups of patients, the usual amount of fluid administered intravenously during the first 24 hours of treatment was between four and six litres.

Insulin Dose

The total insulin doses differed in the two groups of patients; 46% of patients in Group I were given more than 800 units of insulin in the first 24 hours of treatment, as compared with 25% of patients in Group II. In both groups there were two patients who were insulin-resistant, each patient receiving more than 3000 units of insulin during the first 24 hours of treatment.

Alkaline Fluids[1]

One-sixth molar sodium lactate or sodium bicarbonate solution was used as the initial alkaline fluid given intravenously in treatment for 27 (40%) of the patients in Group I, as compared with 24 (75%) of the patients in Group II. The patients who did not receive sodium lactate in this latter group were clinically less severely affected. Five of the patients were children.

Hypokalæmia and Potassium Salts

Hypokalæmia, a plasma potassium level of less than 3 mEq/l. or the presence of classical electrocardiographic changes was observed in 16 patients (24%) from Group I and in four patients (12%) from Group II.

There was also a difference between the two groups of patients with respect to the intravenous administration of potassium salts. In the former group of patients, 38 (57%) received no potassium intravenously during the first 24 hours of treatment, in contrast to 6 (19%) from the latter group of patients. Five of these patients were children and were able to tolerate fruit juices by mouth within the first few hours of treatment. All patients in Group II who were given sodium lactate in the early phase of treatment received more than 50 mEq of potassium intravenously during the first 24 hours of treatment. By contrast, 18 of the 27 patients in Group I treated initially with sodium lactate received no supplementary potassium; 10 of these patients showed frank hypokalæmia during the first 24 hours of treatment.

Causes of Death

The common causes of death in Group I were failure to correct ketosis, as shown by the persistent elevation of the plasma ketone level and depression of the plasma bicarbonate level, hyperglycæmia, and failure of the peripheral circulation with persistent hypotension and oliguria. In addition, at least two patients died in hypokalæmia, with electrocardiographic abnormalities and lowered plasma potassium level at the time of death. There were two examples of insulin resistance in this group. Both patients died, one from unrelieved ketosis and the other from hypoglycæmia following the sudden disappearance of resistance. Two patients were admitted to hospital in a moribund condition, and died within three hours of the commencement of treatment.

The one patient who died in 1956–1957 was a woman, aged 72 years, who showed profound insulin resistance and received 7500 units of insulin over a period of three days. With correction of her ketosis there was a sudden disappearance of insulin resistance, after which she became hypoglycæmic and died.

DISCUSSION

The difference in mortality between the two groups of patients may result from a number of factors—some dissimilarity between the two groups, differences in the type of treatment given or in other details of management, or a combination of all these.

Most recorded observations indicate that the prognosis in diabetic ketosis is worst for elderly, unconscious, hyperglycæmic patients with poor peripheral circulation (Owens and Rockwern, 1939; Rabinowitch *et alii*, 1939; Collen, 1942; Guest, 1949; Greenaway and Read, 1958). Others emphasize that the plasma level of bicarbonate is of less value in assessing prognosis (Kety *et alii*, 1948; Harwood, 1951). In this series of patients similar trends can be observed. If these are accepted as criteria of severity, it would seem that a factor in the reduced mortality of Group II was a lessened severity of ketosis. We believe, however, that this is not the only reason for the sudden decline in mortality during 1956–1957, and that changes in the routine of treatment were also responsible for the reduction in mortality.

Since the severity of diabetic ketosis is related to the presence of coma and peripheral circulatory failure, which are important problems in treatment, some discussion of the causes of these phenomena is indicated. Lowering of the blood pH has been shown experimentally to depress the functions of the central nervous system, the heart and circulation, and the mechanisms that influence insulin action and the peripheral utilization of glucose.

Kety *et alii* (1948) have shown that, although cerebral blood flow was normal or increased in ketotic patients, a close degree of correlation existed between the level of consciousness, depression of cerebral oxygen utilization and lowered blood pH. Schecter *et alii* (1941)

[1] The term "alkaline fluid", although incorrect chemically as it appears in the text, is employed because the expression is accepted through common usage.

demonstrated that hand blood flow and arterio-venous oxygen gradients were diminished in hypotensive ketotic patients. These findings were confirmed by Howarth *et alii* (1948), who showed that cardiac output might be normal or raised in severely ketotic patients with arterial hypotension. In their opinion, the lowered peripheral resistance was due to an opening up of arterio-venous communications, probably in muscle. Lange *et alii* (1951) have shown that lowered blood pH produced by infusion of acid phosphate or gluconic acid is associated with vascular dilatation, lowered peripheral resistance and a fall in diastolic blood pressure.

Although lowering of blood pH has not been convincingly shown to inhibit glucose utilization in man, the work of Haldane *et alii* (1924) suggests that this is so. Using the rat diaphragm, Bornstein and Hyde (1958) have demonstrated a progressive impairment of glucose utilization with lowered pH. Also, Mackler *et alii* (1951) have shown in dogs that acidæmia inhibits insulin action, and the work of Rapoport and Guest (1939) and of Guest (1949) suggests that the functions of other organs and systems are depressed at lowered pH.

The effects of dehydration on the human organism are well known and will not be discussed in detail here. Not only does dehydration accentuate the deleterious effects of acidæmia, but reduced circulating blood volume and decreased peripheral resistance are an undesirable combination if the circulation to vital organs and tissues is to be maintained—particularly to the brain and kidney.

If the basic importance of the correction of acidæmia and dehydration in the treatment of diabetic ketosis is accepted, analysis of the two groups of patients discloses important differences. In both groups the usual amount of fluid given during the first 24 hours of treatment was between four and six litres. The electrolyte solutions administered at the beginning of treatment to the patients in Group I were heterogeneous, and included the following: 5% dextrose with 0·45% sodium chloride solution, 0·9% sodium chloride solution, plasma and blood. By contrast, 75% of patients in Group II received one or more litres of M/6 sodium lactate solution and the remainder 0·9% sodium chloride solution at the commencement of treatment.

Another difference between the groups was the total amount of insulin given in the first 24 hours of treatment (Table I). Although this may possibly reflect a difference in severity between the two groups, another reason may be the early use of sodium lactate in treatment. It is suggested that this has an insulin-sparing effect, the action of insulin being facilitated by the early correction of acidæmia. Although most patients of the former group received similar doses of insulin from the commencement of treatment, there were several cases in which inadequate insulin was used in the presence of continued ketosis and acidæmia.

Comparison of both these aspects of treatment indicates that the routine initial use of alkali and large doses of insulin has contributed to the sharp decline in mortality from severe diabetic ketosis during 1956–1957. Similar trends have been observed in other centres. Thus, most authorities advocate the use of large doses of insulin from the commencement of treatment (Guest, 1949; Harwood, 1951; Root, 1955; Daughaday, 1958), although Lawrence (1955) still denies their value, and Smith and Martin (1954) could not demonstrate any significant advantage of insulin in doses in excess of 40 units per hour. In this respect, however, there were four patients from both groups who required more than 3000 units of insulin for control during the first 24 hours of treatment, and were examples of true insulin resistance. This unusual but important problem has been previously discussed (Field and Stetten, 1956; Downie, 1957).

Correction of acidæmia cannot be achieved rapidly by the use of insulin alone, since it is without effect on those keto-acids already formed. For this reason, alkali is of value in the immediate treatment of acidæmia, and we believe that the initial use of alkali has contributed to the difference in mortality between these two groups of patients. This conclusion receives support from the results of Skillman *et alii* (1958), who showed, during two consecutive five-year periods, a decline in mortality from diabetic ketosis with increasing use of alkaline fluids.

Controversy still exists, however, regarding the use of alkali; some authorities belittle its value (Joslin *et alii*, 1952; Lawrence, 1955), and others do not mention its use (Oakley, 1951; Dunlop, 1953). While there are many advocates for the use of sodium lactate (Guest, 1949; Nabarro *et alii*, 1952*a*; Sprague and Power, 1953; Root, 1955; Colwell, 1957), others favour the use of sodium bicarbonate as being the more physiological (Knowles, 1955; Loeb, 1955). From this series of patients, no conclusions can be drawn about the relative merits of sodium lactate and sodium bicarbonate. We favour sodium lactate, since it is readily available and has the additional advantage of providing lactate, which is an appropriate

substrate for the formation of glycogen in the liver, stores of which are seriously depleted in severe diabetic ketosis.

By means of balance studies on ketotic patients, it has been shown that the loss of intracellular electrolytes is of considerable magnitude (Atchley *et alii*, 1932; Nabarro *et alii*, 1952*b*), and although their correction may be less urgent than that of acidæmia and dehydration, attention must be directed to their replacement from the early stages of treatment. This applies particularly to the restoration of potassium loss, since hypokalæmia can occur as a serious and potentially fatal sequel.

The clinical manifestations of hypokalæmia developing during the treatment of severe diabetic ketosis have been recognized for the past ten or more years (Holler, 1946; Frenkel *et alii*, 1948). It has been shown in the ketotic patient that the potassium deficit may equal or exceed that of sodium, and that it is greater than can be explained by the negative nitrogen balance. In addition, urinary losses may continue during the early phases of treatment (Needham, 1949). It was recognized many years ago that a fall in plasma potassium level may result from insulin action (Briggs *et alii*, 1923). Harrap and Benedict (1924) considered that this was a concomitant effect of the shift of carbohydrate and phosphate into cells. Finally, administration of alkali alone to non-diabetic subjects has been shown to cause a lowering of plasma potassium level (Bellet and Wasserman, 1957).

Therefore, a serious fall in plasma potassium level may be anticipated when a ketotic patient, already potassium-deficient, is treated with large doses of insulin, alkali and a rapid expansion of extracellular fluid. Accordingly, it is now generally accepted that potassium salts should always be administered intravenously in the treatment of patients with severe diabetic ketosis (Danowski, 1955; Lawrence, 1955; Colwell, 1957; Skillman *et alii*, 1958).

The probable relationship between the administration of alkali and the development of hypokalæmia is suggested by the fact that of the 20 patients from both groups who developed hypokalæmia, 19 received M/6 sodium lactate solution as initial treatment. However, the four hypokalæmic patients from Group II received more than 100 mEq of potassium intravenously during the first 24 hours of treatment, without death, whereas 10 patients (67%) from Group I received either no potassium or less than 20 mEq during the first 24 hours of treatment. From these 10 patients there were two deaths in hypokalæmia, and in another three death was associated with hypokalæmia.

From observations from this series of patients, it is important to note that lowering of plasma potassium level may occur at any time from two to 24 hours after the commencement of treatment. It seemed to occur more rapidly if initial treatment consisted of large doses of insulin and alkali. Thus, four patients from Group II became hypokalæmic within the first four hours of treatment, whereas in Group I, in which the initial doses of insulin and sodium lactate tended to be smaller, lowering of plasma potassium level occurred at any time up to 24 hours after the start of treatment. Further, our impression was that the rate of lowering was clinically more important than the level to which the plasma potassium level was depressed.

Certain conclusions may be drawn from these comparisons. Hypokalæmia is an important factor in the overall mortality of severe diabetic ketosis, and steps taken to prevent, recognize and treat this condition will reduce mortality. The incidence of the potentially fatal complication is highest in any régime that uses large doses of insulin and alkali early in treatment. The regular intravenous use of large amounts of potassium salts has probably contributed to the decline in mortality shown in the latter group of patients. Hyperkalæmia was not encountered in any patient after such treatment.

Although the delayed development of sudden vasomotor collapse has been described as a cause of death in diabetic ketosis (Daughaday, 1958; Greenaway and Read, 1958), no example was encountered in this series. However, there were a number of patients, hypotensive on admission to hospital, who showed some response to initial treatment but subsequently collapsed. On retrospective analysis, all these cases appeared to be associated with uncorrected acidosis, hypokalæmia or hypoglycæmia. In some, serum or blood was used without effect, and in others the addition of nor-adrenaline to the fluid given intravenously produced a rise in blood pressure which was not sustained.

Observations on this present series of patients do not permit conclusions to be drawn about the use of special electrolyte solutions once acidæmia has been overcome and dehydration corrected. All patients in both groups were given solutions of sodium chloride or destrose with or without added potassium salts. Although serial plasma electrolyte determinations have been used to control this phase of treatment, hyperchloræmia was noted on several occasions in patients from both groups. Such a complication adds to the acidosis, and is a reasonable indication

for the use of electrolyte solutions in which the ratio of concentrations of sodium and chloride approximates more closely to that of extracellular fluid. Such solutions have been described by Butler (1950) and by Nabarro *et alii* (1952*a*).

Comparison of the two groups of patients shows that a substantial decline in mortality has been associated with treatment that is directed toward the urgent correction of acidæmia and dehydration and the prevention of hypokalæmia. However, no claim is made that these are the only factors associated with this decline in mortality. Attention has already been drawn to the possible differences in severity of the condition between the two groups of patients.

Another difference between these groups of patients has been a change in the responsibility for their management. This present study commenced in 1956, from which time all patients with severe ketosis have been admitted to hospital in the care of a single unit which had shared in the experience of the previous four years.

Strict adherence to the principles laid down is not a substitute for continuous attention to detail at the bedside during the first few hours of treatment. As Daughaday (1958) has indicated, "survival of the patient is often dependent upon some 'trivial' aspect of treatment". We would completely agree with this and add that not the least of these aspects is the training of nurses in the proper care of these patients, so that treatment can be planned and executed more efficiently in a ward whose staff is familiar with the problem.

It is of interest that patients admitted to hospital during the last two years were, in general, less severely affected than those of earlier years. In common with other centres, patients have frequently arrived at this hospital in a moribund condition that has resulted from misunderstanding and mismanagement prior to their admission. A number of mistakes occurred from failure to recognize the condition or, if it was recognized, to appreciate the consequences. Other authors have encountered similar problems (Burston, 1958; Taft, 1958). With the introduction of simplified procedures, there can be no excuse for failure to test urine for glucose and ketones. This emphasizes the fundamental problem of the education of both patients and practitioners in the prevention and recognition of ketosis, so that patients arrive at hospital in a condition that permits the correction of ketosis with simple measures.

In conclusion, we wish to draw attention to the comments of Sprague and Power (1953):

> It is true that most patients still recover from diabetic acidosis, as they have done for many years without precise attention to deficiencies of potassium or to the finer details of replacement. This, however, is not sufficient reason for ignoring these aspects of treatment, for there is no reliable way of separating the majority of patients for whom these aspects are unimportant from the minority for whom they are of vital importance.

Certainly our aim must be the detection and successful treatment of this minority.

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HUMORAL FACTORS IN LIVER REGENERATION[1]

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SUMMARY

The mechanism by which control of growth in multi-cellular organisms is exercised is ill understood. Previously, it was thought that this was due to some " work " factor. However, it has been shown that injection of a rat with serum taken from a partially hepatectomized rat results in an increased mitotic rate in the liver of the recipient rat. When serum taken from partially hepatectomized rats is subjected to Cohn-type fractionation, the active agent(s) has been found to be associated with the alpha-globulin and albumin fractions.

LIVER REGENERATION is an important phenomenon in most liver diseases, since on this, particularly when there has been considerable destruction of parenchyma, the survival and future activity of the individual depend. Consequently, the nature of the fundamental processes involved have deservedly received much attention.

At present, little is known concerning the mechanisms by which stimulation of and control over growth in multi-cellular organisms is achieved. Regeneration of the remaining liver follows partial hepatectomy in the rat. It was previously thought that this was due to some " work " factor. However, by the use of parabiotic rats, it has been shown that after partial hepatectomy in one partner there is an increase in hepatic mitoses in the other (Bucher *et alii*, 1951). This suggests that a humoral pathway is involved in the regulation of growth. However, experiments using parabiotic rats cannot distinguish whether this effect is due to the appearance of a circulating mitosis-stimulating factor or to the fall in blood concentration of an agent responsible for inhibition of liver mitosis.

Friedrich-Freksa and Zaki (1954) have found that the intraperitoneal injection of serum taken from partially hepatectomized rats induces an increase in liver mitoses in the recipient rat. The factor responsible was found to be non-dialysable, organ-specific (at least in regard as its failure to induce mitoses in parotid gland epithelium—Swann, 1957) and possibly species-specific (not active on mouse liver).

Initially, attempts were made to repeat this work, and on confirmation of the observation that injection of serum from recently hepatectomized rats caused cellular growth (as shown by increased mitotic figures) in a normal animal, experiments were performed to attempt to elucidate which serum fractions contained the active substance. The results of these experiments are reported here.

METHODS

The rats used were of Wistar strain weighing 120 to 180 grammes, and were fed a stock diet of " Barastoc " (a local proprietary food) *ad libitum*.

Partial hepatectomy was performed by the methods of Higgins and Anderson (1931). Forty-eight hours after operation, the rats (under ether anæsthesia) were bled into axillary pouches. The blood obtained was allowed to clot and stand in a refrigerator. Amounts of 1 to 5 ml. of the serum obtained were injected intraperitoneally into normal rats of the same age. As a control, other similar rats were injected with normal rat serum. After a further interval of 24 hours the recipient rats were sacrificed and thin slices of their livers fixed either in 10% formol saline or in the following fixative: Bouin's fluid with acetic acid, 100 ml.; urea, 2·0 grammes; chromium trioxide, 1·5 grammes.

After the chromium trioxide had been added, the fixative was used as soon as it cooled. After routine embedding in paraffin, sections were cut at 5μ and stained with hæmatoxylin and eosin.

Mitotic figures were counted by means of a ×10 ocular and ×40 objective. The average number of parenchymal cells per field was 128. In each case 100 fields were examined, giving a total of 12,800 cells per liver (animal) scanned. Only definite mitotic figures from late prophase onwards were counted. Initial experiments confirmed the findings of Friedrich-Freksa and Zaki (1954) but intraperitoneal injection of post-hepatectomy rat serum induced increased hepatic mitotic activity in other rats (see results). However, the dosage of serum required was higher (greater than 5 ml.) and the level of induced mitotic activity was lower than that found by these authors.

Efforts were made to determine in which serum fraction the active material resided. Accordingly, pooled serum from partially hepatectomized rats (25 ml. batches) and from normal rats was subjected to Method 10 Cohn fractionation (Cohn *et alii*, 1950). The initial fractions I+II+III, IV+V and VI (after being freed of bivalent cations and ethanol by addition of citrate and dialysis) were each reconstituted in 25 ml. of normal saline, and amounts of 5 ml. were injected

[1] Received on June 10, 1959.
[2] Research Fellow.

intraperitoneally into normal rats. Liver sections from the recipient rats were prepared and examined as before. As the mitosis-stimulating fraction appeared to be concentrated in fraction IV+V (see results), further pooled post-hepatectomy serum was fractionated into fractions IV+V. These fractions were each reconstituted in the original serum volume of normal saline, and quantities of 5 ml. were injected intraperitoneally into normal rats. Liver sections were prepared and examined as before.

RESULTS

Tables I and III show the incidence of mitotic figures in livers of rats injected with either normal rat serum or fractions of normal rat serum. A total of nine mitotic figures was found in the livers of 20 animals. This amounts to a mitotic frequency of three per 100,000 cells, and corresponds with the mitotic frequency of five to 10 per 100,000 cells as given by Brues and Marble (1937) in normal rats. The mean mitotic frequency per 12,800 cells was 0·5, standard deviation 0·1.

TABLE I

Incidence of Mitotic Figures in Livers of Rats Injected with Normal Rat Serum

Experiment Number	Quantity of Serum Injected (Millilitres)	Number of Mitotic Figures per 12,800 Cells
1	1	1
2	2	—
3	3	—
4	3	1
5	4	2
6	4	—
7	5	—
8	5	—

TABLE II

Incidence of Mitotic Figures in Livers of Rats Injected with Serum from Partially Hepatectomized Rats

Experiment Number	Quantity of Serum Injected (Millilitres)	Number of Mitotic Figures per 12,800 Cells
9	1	1
10	2	2
11	2	2
12	3	1
13	3	4
14	4	5
15	4	3
16	5	13
17	5	17
18	5	12
19	5	11

For rats injected with 5 ml. of whole serum from post-hepatectomized rats, the mean mitotic frequency was 13, standard deviation 1·0. Rats injected with 1 to 4 ml. of whole serum from post-hepatectomized rats showed a mean mitotic frequency of 2·6, standard deviation 0·6. Subsequent examination of the livers of rats injected with post-hepatectomy serum protein fractions prepared by method 10 of Cohn *et alii* (1950) showed little or no activity above that of the controls in those rats injected with fractions I+II+III and with fraction VI.

TABLE III

Incidence of Mitotic Figures in Livers of Rats Injected with Serum Fractions; Each Derived from 5 ml. of Normal Rat Serum

Experiment Number	Serum Protein Fraction X (Cohn *et alii*, 1950)	Number of Mitotic Figures per 12,800 Cells
20	I+II+III	0
21	I+II+III	1
22	I+II+III	0
23	I+II+III	0
24	IV+V	1
25	IV+V	1
26	IV+V	0
27	IV+V	1
28	VI	0
29	VI	0
30	VI	1
31	VI	0

TABLE IV

Incidence of Mitotic Figures in Livers of Rats Injected with Serum Fractions; Each Derived from 5 ml. of Serum from Partially Hepatectomized Rats

Experiment Number	Serum Protein Fractions (Cohn *et alii*, 1950)	Number of Mitotic Figures per 12,800 Cells
32	I+II+III	2
33	I+II+III	1
34	I+II+III	2
35	I+II+III	1
36	I+II+III	1
37	IV+V	8
38	IV+V	9
39	IV+V	11
40	IV+V	8
41	IV+V	12
42	VI	1
43	VI	0
44	VI	0
45	VI	1

TABLE V

Incidence of Mitotic Figures in Livers of Rats Injected with Serum Fractions; Each Derived from 5 ml. of Serum from Partially Hepatectomized Rats

Experiment Number	Serum Protein Fractions (Cohn *et alii*, 1950)	Number of Mitotic Figures per 12,800 Cells
46	IV	4
47	IV	8
48	IV	10
49	IV	4
50	IV	11
51	V	9
52	V	7
53	V	11
54	V	13
55	V	9

On the other hand, those rats injected with fractions IV+V showed an average mitotic count of 9·6, standard deviation 0·6. Subsequent fractionation of fractions IV+V by the Cohn procedure into fraction IV and fraction V failed to resolve the active substance into a single fraction. The mitotic frequency of rats injected with fraction IV showed, per 12,800 liver cells, an average count of 7·4, standard deviation 1·3, and of fraction V 9·8, standard deviation 1·1.

DISCUSSION

These experiments confirmed the findings of Friedrich-Freksa and Zaki (1954) that injection of a rat with serum taken from a post-hepatectomized rat induced increased mitotic activity in the liver of the recipient rat. The actual dosage of serum required was higher and the number of mitotic figures induced lower in these experiments than those of Friedrich-Freksa and Zaki (1954). This may be due to strain differences in the rats used, or to differences in the criteria of counting. In fractionating the serum by the Method 10 of Cohn, the active material was associated with the alpha-globulin and albumin fractions. It could well be, however, that some growth hormone associated as a prosthetic group with these proteins concerned. No further investigations to determine the tissue specificity of this stimulating factor have been carried out, and in the light of the discussion of Swann (1957), several other organs besides parotid gland will have to be investigated before a claim that the factor is organ-specific can be made. The results of these experiments, and of those of Bucher *et alii* and of Freidrich-Freksa and Zaki (1954), suggest that the formation of a humoral growth-stimulating substance is associated with partial hepatectomy. On the other hand, Glinos and Gey (1952), after studying the effect of addition of rat serum to tissue cultures and of mitosis in the livers of rats which had been plasmaphoresced, concluded that serum contained an inhibitor to liver growth, and that the concentration of the inhibitor was decreased after partial hepatectomy. Kohn (1958) investigated the effect of administration of normal rat serum and sera from laparotomized and partially hepatectomized rats on the liver regeneration following partial hepatectomy. He found that doses in excess of 1 ml. every 12 hours of serum from normal or laparotomized animals had an inhibitory effect on liver regeneration. This result was significant at the 5% level. As no significant differences were observed between animals receiving serum from laparotomized rats and those receiving serum from partially hepatectomized rats, Kohn (1958) concluded that rat serum contains a factor or factors which inhibit liver growth *in vivo*. Kohn (1958) used increase in liver size and not mitotic figure counts as a criterion of growth.

Saetren (1956) has removed parts of organs and then returned macerates of the organs concerned into the peritoneal cavity of rats. In this way he has inhibited regeneration of the organs in question. He finds the effects are tissue-specific, and postulates the local concentration of an "*m*-inhibitor" for each organ. The concepts of mitosis-stimulating and mitosis-inhibiting factors are not mutually exclusive, and both may play a role in the overall mechanism of growth control.

ACKNOWLEDGEMENT

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ANÆMIA OF RENAL ORIGIN, STUDIED BY MICRODISSECTION OF THE KIDNEY[1]

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SUMMARY

Clinical data and animal experimentation imply that the kidney may be the site of formation of a substance responsible for normocyte maturation and the release of erythrocytes from bone marrow.

A quantitative and qualitative study by means of microdissection of nephrons has been carried out on the kidney from a four months old infant, G.K., who had suffered from severe anæmia and renal disease since birth.

The dimensions of nephrons in the baby G.K. are compared with those from a normal baby.

The changes in the anatomy of the nephron include variations in size and shape of glomeruli, hypertrophic proximal tubules, and very short loops of Henle. In addition, two types of atrophic tubules, blind-ending collecting tubules, diverticula and cysts were found.

In this patient G.K., the short loops of Henle were found universally throughout the kidney. In the normal subject, the loop of Henle may prove to be the site for the formation of the erythrocyte-stimulating factor, and in the present subject, the absence of the loop may have been an important factor in the causation of the anæmia.

ANÆMIA associated with chronic renal disease is a well-recognized clinical entity. Rose (1952), in a series of anæmic patients with poor renal function, found that anæmia of renal origin was a common condition in adults, being five times as common as Addisonian pernicious anæmia.

The anæmia is normocytic and normochromic; the bone marrow is either hyperplastic or normal, never depressed. Two basic faults—failure of maturation of normoblasts and inhibition of the mechanism of release of red cells from the bone marrow—contribute to the anæmia. By contrast polycythæmia, affecting the red cells only, occurs in patients with renal tumours. These features support the hypothesis that an erythrocyte-stimulating substance is produced by the kidney (Conley *et alii*, 1957; Damon *et alii*, 1958).

A new-born baby, G.K., was found to be anæmic immediately after birth. No cause for the anæmia could be found apart from multiple renal anomalies. A localized deficiency in the tubules was revealed by the microdissection technique. It is possible that this predominant structural tubular abnormality is responsible for a lack of the erythrocyte-stimulating substance and the consequent anæmia. Other changes in nephron anatomy have been recorded, but the significance of these is not yet apparent.

[1] Received on August 3, 1959.
[2] Surgical Research Fellow.

CASE HISTORY

The male baby G.K., whose birth weight was 2·3 kg., was born three weeks prematurely. He was admitted to hospital three hours after birth because of extreme pallor. His hæmoglobin value was 8·0 grammes per 100 ml. He was not jaundiced, and the spleen was not palpable. His blood group was O, Rh-positive; direct and indirect Coombs tests produced negative results. Microscopic examination of the urine revealed no abnormality. There was no occult blood in the stool or any other evidence of bleeding. A blood transfusion was given, and he was discharged from hospital three weeks later with a hæmoglobin value of 13·0 grammes per 100 ml.

He was readmitted at the age of eight weeks because of weakness, difficulty in sucking, and vomiting. He was pale and afebrile, and on the right side of the abdomen a mass, thought to be of renal origin, was palpated. His blood urea content was 99 mg. per 100 ml., and an intramuscular pyelogram revealed a large right-sided hydronephrosis. At the age of four months he died. His hæmoglobin value had fallen to 7·3 grammes per 100 ml., and the blood urea level had risen to 118 mg. per 100 ml.

POST-MORTEM FINDINGS

Necropsy revealed abnormalities of the urinary tract (Figure I), a valvular patency of the foramen ovale, an accessory thumb, and a right inguinal hernia.

The left kidney was small (5 cm. by 2 cm. by 1·12 cm.), and moderate dilatation of the renal pelvis was observed. At the pelvi-ureteric junction there was a constriction; the first part of the ureter then expanded in a globular fashion to about three times the normal diameter; this expansion was followed by a further constriction. Both constrictions appeared to be non-obstructive, measuring approximately 0·2 cm. The rest of the ureter was of normal calibre, but slightly thickened.

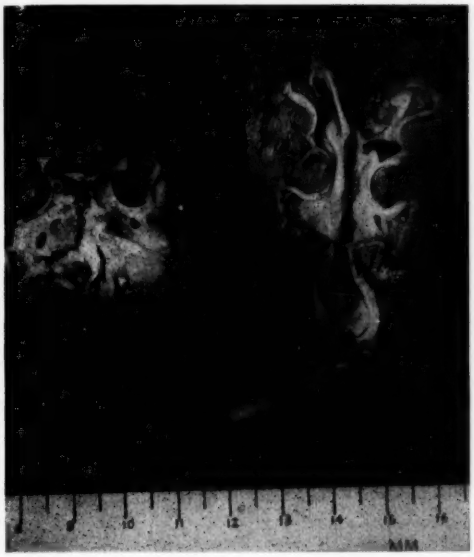

FIGURE I

Part of the right kidney, showing several cysts. The left kidney shows moderate dilatation of the pelvis, and the two constrictions in the ureter with the globular dilatation between them

FIGURE II

The large irregular cysts in dense collagenous material in the right kidney. (×125)

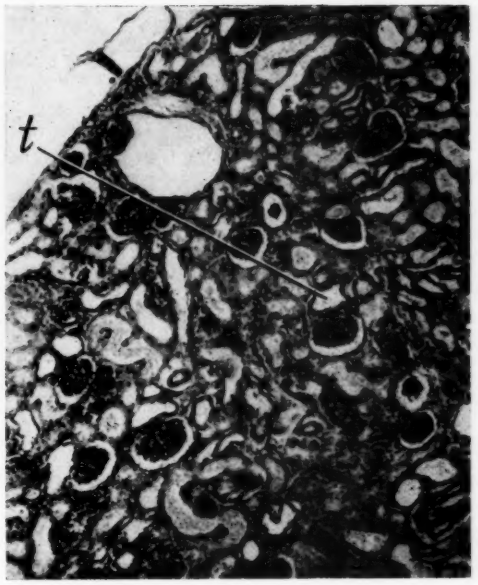

FIGURE III

The subcapsular cortex of the left kidney, showing a glomerular cyst and a collecting tubule (*t*) with darker nuclei, ramifying into the subcapsular cortex. (×125)

FIGURE IV

The medullary zone of the left kidney, showing the general increase in diameter of all tubules, especially collecting tubules. (×125)

FIGURE V

The large oval glomerulus and well-convoluted proximal tubule on the right-hand side, contrasted with the small unit at the left. Note the presence of dense casts (*C*) within the lumen of the proximal tubule. (×50)

FIGURE VI

A glomerulus and proximal tubule broken (during dissection) at the beginning of a short, poorly-differentiated Henle's loop. (×50)

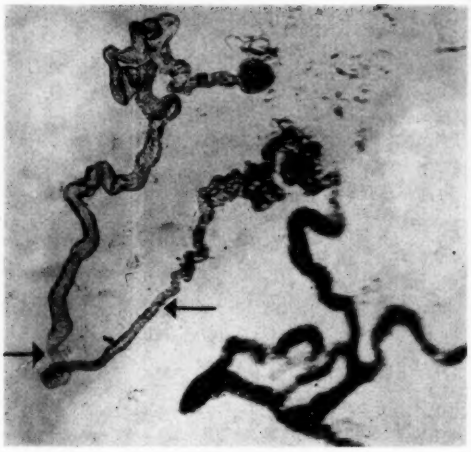

FIGURE VII

A small entire nephron. The segment of tubule between the arrows represents the poorly differentiated loop of Henle. (×50)

FIGURE VIII

A group of normal distal convoluted tubules joined to form a collecting tubule. (×50)

FIGURE IX

Two types of atrophic glomeruli and proximal tubules. Left: a straight undifferentiated tubule following the glomerulus. Right: the tubule has retained its convoluted structure. (×50)

FIGURE X

Very small, almost transparent glomerulus and straight undifferentiated tubules found deep in the juxtamedullary cortex. (×100)

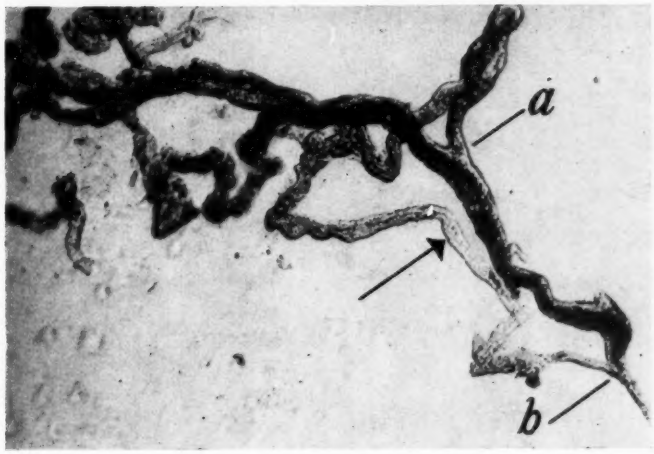

FIGURE XI

The tubule (arrow) is a convoluted tubule which opens from the collecting tubule at point (*a*) and enters the same collecting tubule at point (*b*). (×50)

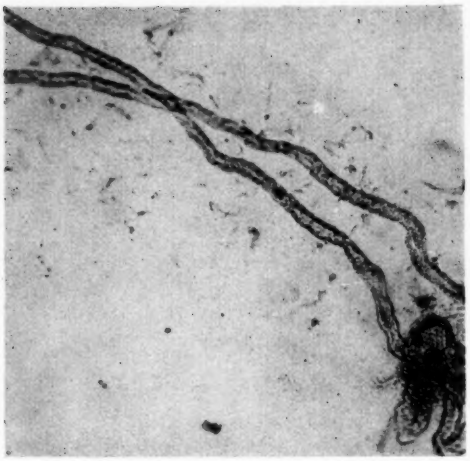

FIGURE XII
U-shaped ductules, with the convoluted wider segment joining the two arms of the U. (×50)

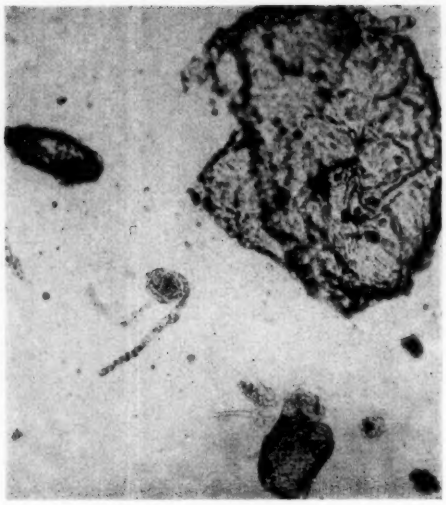

FIGURE XIV
A large, thin-walled cyst at the upper right-hand corner; smaller cysts with walls of varying thickness; atrophic glomerulus and narrow first part of proximal tubule. (×50)

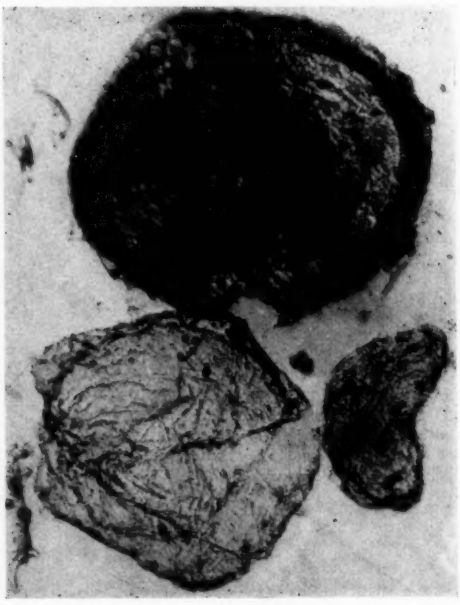

FIGURE XIII
Three cysts, probably glomerular in origin, showing the varying translucency of the thickness of their walls. (×50)

FIGURE XV
A large irregular cyst on the left alongside a broken glomerulus and proximal convoluted tubule. (×50)

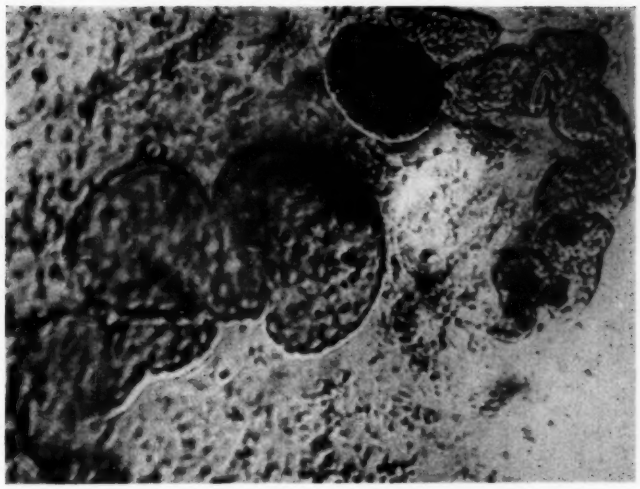

FIGURE XVI

Very thin, irregular cyst, of possibly tubular origin, with a glomerulus and first part of proximal convoluted tubule in the upper left-hand corner. (×200)

The right kidney (6 cm. by 3·5 cm. by 2·5 cm.) was composed of a mass of cysts from which a very fine ureter coursed to the bladder. Cysts varied in size from 1·5 cm. in diameter to those just visible to the naked eye. Fluid from three of the larger cysts was analysed for protein, creatinine and urea content, with the results shown in Table I.

TABLE I

Cyst Number	Protein Content[1]	Creatinine Content	Urea Content
1	1·4	4·1	380
2	1·2	3·8	304
3	3·6	3·9	240

[1] Protein, creatinine and urea contents in milligrammes per 100 ml.

Microscopic Examination

The microscopic findings are shown in Figures II, III and IV.

In the left kidney there was an overall diminution in nephrons. The glomeruli and tubules were larger in diameter than in the normal. Tubules with the appearance of collecting tubules ramified high up into the thinned cortex. Glomerular cysts containing tuft remnants could be identified. There was very little increase in interstitial connective tissue and no evidence of inflammatory infiltration. The blood vessels appeared normal.

The right kidney was almost entirely replaced by numerous thin-walled cysts lined by cuboidal or columnar epithelium containing large, deeply basophilic round nuclei. The cysts were separated by dense collagenous material, in which a few scattered round cells were visible (Figure II). These cystic spaces appeared to be histologically similar to the tubules

TABLE II

Measurements of the Nephrons and Cysts

Specimen	Normal 3 Months Infant	G.K., Anæmic 4 Months Infant (Born Three Weeks Prematurely)
Glomerulus[1]	96μ	140μ
Proximal convoluted tubule[1]	Short, 32μ × 1·3 mm.; long, 43μ × 2·6 mm.	64μ × 3·7 mm.; 32μ × 1·3 mm. (atrophic convoluted); 13μ (atrophic straight)
Loop of Henle:		
Narrow	Short, 13μ × 2·6 mm.; long, 3·7 mm.	25·6μ × 0·6 mm.
Wide[2]	Short, 32μ × 1·3 mm.; long, 3·7 mm.	40μ × 0·6 mm.
Distal convoluted tubule[2] ..	Short, 26μ × 1·3 mm.; long, 2·6 mm.	40μ × 2·6 mm.
Collecting tubules[2]	Short, 43μ × 1·3 mm.; long, 64μ × 2·6 mm.	64μ × 2·6 mm.; 96μ × 3·2 mm.; 128μ (incomplete); 196μ (incomplete)
Abnormal structures ..		Cysts: 512μ × 512μ; 256μ × 256μ; 256μ × 896μ; 128μ × 256μ Ductules: 25·6μ to 96μ to 64μ, length 5·12 mm.

[1] Measurements of glomeruli and proximal tubules are the average of 50 recordings.
[2] Measurements of loops of Henle, distal tubules and collecting tubules are the average of five readings.

FIGURE XVII
At the arrows, the collecting tubules exhibit a sudden widening in diameter when the distal convoluted tubules join. (×50)

FIGURE XVIII
Showing sudden widening and narrowing of collecting tubule diameter without any apparent cause (arrows). (×50)

FIGURE XIX
At the arrow, sudden widening of the diameter of a collecting tubule where the distal convoluted tubule joins. (×50)

FIGURE XX
Distal convoluted tubule, showing a large diverticulum (*d*). (×50)

FIGURE XXI
A blind-ending distal convoluted tubule (arrow). (×100)

described by Ericsson *et alii* (1958) in the cases of renal dysplasia. Where solid renal parenchyma was scattered sporadically between these cystic structures, it appeared to be the same as described for the left kidney. The lumen of the right ureter was patent on microscopic examination.

In summary, cystic changes on the right side almost entirely replaced the kidney. A few scattered islands of recognizable tissue were similar to those on the left side. The renal parenchyma of the left kidney showed increase of diameter of the remaining nephrons, which were fewer in number than in a normal section. There was no evidence of infection.

Findings on Microdissection of the Left Kidney.—The microdissection method of Oliver *et alii* (1951) was used mainly, though the modification suggested by Ritchie and Waugh (1957), with longer maceration at refrigeration temperature, was also employed. Both the methods gave similar results; but the difficulty of correct timing of maceration still poses a major problem.

The nephrons in the main were larger in diameter and in length than in the normal subject (see Table II). There was considerable variation in the size and shape of glomeruli, with gradations to that of cyst formation. The glomerular shapes were round or ovoid (Figures V, VI, VII, IX and XIV). The average diameter was 140μ. Approximately one glomerulus in 20 was small and atrophic; diameters as small as 32μ were recorded. Intermediate sizes were not uncommon, and diameters of 64μ, 90μ and 120μ were recorded. There were cysts of large and intermediate sizes of glomerular and possibly tubular origin (Figures XIII, XIV, XV and XVI and Table II).

The proximal tubules varied considerably in the degree of convolution. Some tubules were poorly convoluted, some were normal. Cast material within the lumen was a prominent feature, often extending to the neck segment of the tubule (Figures V, VI and XXII). The dilatation of the lower ends of the proximal tubes was often twice that of the upper ends.

Of the small atrophic nephrons two types were seen, one with normal convoluted tubular pattern (Figure VII), the other short and straight. This second type was seen only deep in the cortex (Figures IX and X).

Loops of Henle were all replaced by very short, straight segments between the proximal and distal convoluted tubules. The usual subdivision into narrow and wide parts of Henle's loops was not well marked (Figure VII).

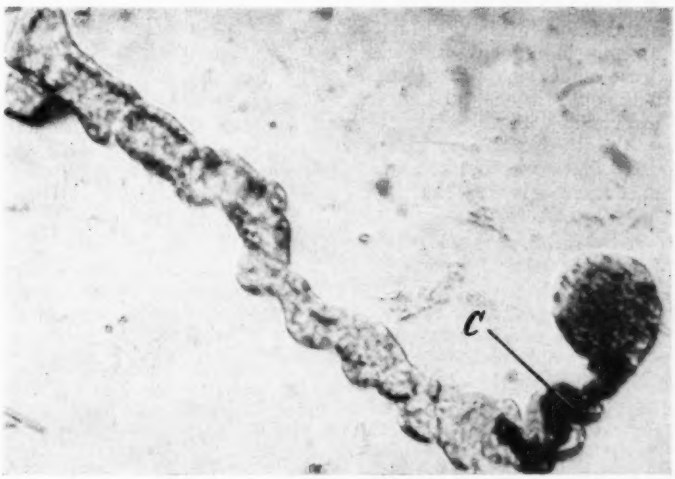

FIGURE XXII
A round glomerulus and proximal convoluted tubule containing dense cast (*C*) at the neck of the tubule. (×100)

The distal convoluted tubules showed little variation from the normal (Figure VIII).

The collecting tubules, ramifying as far as the subcapsular cortex and often showing curious variations in diameter and stippling, were features of this material. At the point of entrance of the distal tubule into the collecting tubule, sudden widening of diameter occurred (Figures XVII, XVIII and XIX).

Two types of unusual tubular variants were observed. The first group included convoluted tubules, opening at one end into a collecting tubule and again reentering the same collecting tubule at a lower level. No connection with a glomerulus and no true subdivision into the usual nephron components could be found in these strange tubules (Figure XI).

The second group of tubules consisted of long U-shaped ductules. A very short, wider segment of convoluted tubule connected the straight long arms of the U. These ductules appeared to have no connexion with the collecting system or with glomeruli. Average figures for three ductules are given in Table II. These ductules were translucent, and showed only a sparse stipple pattern.

Blind-ending collecting tubules were observed (Figure XXI). These ends were slightly expanded, but showed no gross dilatation. Diverticula were common, especially along the collecting tubules. These often had narrow necks connecting them with the collecting tubules (Figure XX).

Cysts were seen to be both of tubular and glomerular origin, thick and thin walled (Figures XIII, XIV, XV and XVI), and with and without tubular connexions.

Discussion

No cause for the anæmia was found, apart from the intrinsic renal anomalies. Anæmia of chronic renal disease has been found in association with many other renal lesions, including nephrosclerosis, malignant hypertension, polycystic disease, chronic pyelonephritis and obstructive surgical renal conditions.

In 1933, Parsons and Ekola-Strolberg demonstrated that the anæmia in renal disease was associated with azotæmia. However, the anæmia is never a hypoplastic one, so that it is unlikely to be associated with the action of toxic products on the bone marrow. Platt (1952) demonstrated that, of the retained products in azotæmia, anæmia is not related to high levels of urea, creatinine or phosphate.

Experimental work by Jacobsen *et alii* (1957) and Naetes (1958), and the clinical reports by Conley *et alii* (1957) and Damon *et alii* (1958), suggest that the kidney is probably the site of formation of a substance which is essential for the maturation of normoblasts and for the release of mature erythrocytes from the bone marrow.

Measurements by microdissection of the nephrons of the baby G.K., when compared with those from the normal control kidney, indicate a generalized marked decrease in the length of the loops of Henle. This difference is approximately 5 mm.

Few data are available on the development of different parts of the nephron. Keibel and Mall (1912) quote Toldt (1874) as stating that differentiation into wide and narrow segments of the loops of Henle takes place as early as the fourth month of fœtal life.

The existence of short undifferentiated loops of Henle has been recorded in the neonate by McCance (1948) on histological data. Bialestock (1958) described this feature in one of the kidneys of a baby, aged one month, with pyelonephritis studied by microdissection.

In the present study, the only functioning part of the nephron universally deficient is the loop of Henle. It is suggested that in the normal kidney this may be the site of formation of the erythrocyte-stimulating factor, and the absence in this case may be a causative factor in the anæmia.

The other diverse renal changes observed during microdissection seem less likely to explain the anæmia, for such abnormalities have been found in the only functioning parenchyma of other patients in whom anæmia was not a factor.

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MORPHOGENESIS OF UNILATERAL MULTICYSTIC KIDNEY IN CHILDHOOD[1]

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SUMMARY

The clinical details of a child R.W., aged 13 months, in whom an abnormal cystic kidney was excised, are recorded.

The microdissection study of this kidney revealed that some of the nephrons were quantitatively comparable with those of a normal kidney from a child of the same age.

Failure of union at the site of junction of distal convoluted tubules and collecting tubules of the nephrons was demonstrated in about one-third of the nephrons studied. These observations support the embryologists who consider that the excretory and collecting systems are formed separately and unite at this junction.

All the abnormalities observed could not be explained by this simple mechanical explanation.

The adverse stimuli responsible for the cystic changes in this kidney were probably active after the renal system had already normally differentiated. This would indicate that the morphogenesis of this condition, unilateral cystic disease in infancy, should be regarded as different from that of polycystic disease. Clinically, such a differentiation has been suggested by all the other reports of unilateral multicystic kidney.

UNILATERAL cystic disease of the kidney is an uncommon condition. Most of the recorded cases have been in infants and children.

Reviews by Spence (1955), Coppridge *et alii* (1958) and Beltran (1959) have all emphasized that clinically, macroscopically and histologically this condition can be differentiated from bilateral cystic conditions of the kidney.

Microdissection studies in the case to be described suggest that the morphogenesis of unilateral multicystic renal disease presents differences from that previously formulated for polycystic renal disease (Bialestock, 1956).

Confusion exists in the terminology of cystic conditions of the kidney. In this paper, the term "multicystic disease" is being used to denote an irregular unilateral collection of cysts involving most of one kidney. The term "polycystic disease" refers to that bilateral condition, often with a familial incidence, in which the reniform shape is maintained, and which is seen in the new-born infant and in young adults.

The importance of separation lies in differences seen morphologically and in the prognosis. The prognosis of bilateral familial polycystic disease is uniformly poor, and that in unilateral multicystic disease invariably favourable.

[1] Received on August 20, 1959.
[2] Surgical Research Fellow.

CASE HISTORY

R.W., a female child, aged 13 months, was first examined at the age of 11 months because of an attack of gastro-enteritis. A mass was palpable in the right loin. X-ray investigation revealed a non-functioning kidney on the right side and a normal kidney on the left side. The right ureter or its orifice could not be identified at cystoscopy.

At operation, the right renal mass was excised together with a kinked, narrow, beaded ureter, which appeared to be the site of multiple areas of atresia. Distally, the ureter ended as a thin, hair-like structure several centimetres in length.

The excised kidney measured approximately 6 cm. by 3 cm. by 3 cm. It consisted of two distinct types of tissue— an irregular mass of cysts and a small segment of solid tissue. The cysts varied from 5 cm. in diameter to a size invisible to the naked eye. The small piece of solid tissue measured 1 cm. by 0·5 cm. by 0·5 cm., and lay wedged between the cysts.

No true pelvis could be identified. The renal mass had no demonstrable patent communication with the narrow ureter.

Routine histological examination of the right renal mass revealed that the cysts, large and small, were lined by a single layer of flattened columnar epithelium, and were surrounded by dense collagenous material. The solid tissue was composed of normal glomeruli and tubules heavily infiltrated with small round cells, but without any increase in interstitial tissue between the nephron components.

Examination of sections of the ureter showed the presence of a lumen along most of its length. The lumen of the distal 0·5 cm. of the terminal narrow segment was completely obliterated.

Microdissection

Microdissection by the method previously described (Bialestock, 1956) was performed on the cystic mass

FIGURE I

The normal glomerulus and convoluted proximal tubule illustrate the presence of the normally developed structures in the grossly disorganized kidney. (×50)

FIGURE II

Collecting tubule of normal pattern, with a distal convoluted tubule between the two arms of the Y. (×50)

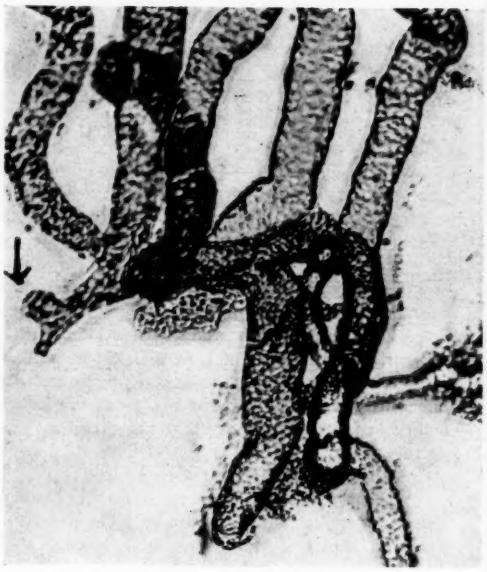

FIGURE III

The junction of a number of blind-ending collecting tubules is shown. Note the widening and thinning of the cells to give a more transparent appearance than in Figure II. The only terminal blind end in this illustration can be seen halfway along the left side of the illustration (arrow). (×50)

FIGURE IV

This demonstrates (arrow) the upper blind curved end of a collecting tubule from the group of abnormal collecting tubules shown in Figure III. (×100)

TABLE I

Nephron Measurements in Right Kidney of R.W. and of a Normal Baby Aged 13 Months[1]

Specimen	Glomerulus	Proximal Tubule	Loop of Henle		Distal Convoluted Tubule	Collecting Tubule
			Narrow	Wide		
Small solid nubbin of right kidney of R.W., aged 13 months	128μ	42μ × 4·5 mm.	13μ × 2·9 mm.	26μ × 2·9 mm.	30μ × 3·2 mm. (incomplete)	32μ–64μ × 3·2 mm. (incomplete)
Normal kidney from baby aged 13 months	96μ	42μ × 5·1 mm.	13μ × 5·1 mm.	26μ × 3·8 mm.	30μ × 4·5 mm.	32μ–64μ; no length measured

[1] Figures for glomeruli and proximal tubules are the average of 10 measurements. Those for other parts of the nephron are single measurements only.

and on the solid nubbin of renal tissue. The nephron dimensions were compared with those obtained from a normal kidney of a child of the same age (13 months).

Most of the renal mass was composed of round cystic structures. The cysts showed considerable variation in size, from those visible to the naked eye, to minute microscopic structures only a little larger than normal glomeruli. No connexion between these cysts and tubules could be demonstrated. This was an unusual finding, as in other material studied cysts often showed some tubular connexions, or the cysts were composed of tubular and glomerular parts.

The solid nubbin of tissue was composed of normal and abnormal structures. In this tissue, all the glomeruli and proximal tubules (Figure I) and loops of Henle were normal. Both normal and abnormal distal convoluted tubules and collecting tubules were identified. About two-thirds of the normal distal convoluted tubules opened directly into the first collecting tubules without any loss of continuity of the tubular lumen (Figure II).

The remaining distal convoluted tubules showed a characteristic anomaly. The abnormal structures consisted of masses of thin-walled, blind-ending, slightly dilated collecting tubules lying adjacent to, but not in continuity with, thin attenuated tubules which represent ends of distal convoluted tubules (Figures III and IV). The total lack of any connexion between the convoluted tubular system with the collecting system suggests an embryological basis for the anomaly.

DISCUSSION

The present history and findings appear typical of the condition unilateral cystic kidney; that is, a child well but for occasional gastro-intestinal symptoms is found to have a palpable mass in one loin.

Investigations show a non-functioning kidney on one side and a normal kidney on the other. The differential diagnosis lies between a Wilms's tumour, a large hydronephrosis and a cystic kidney. At operation the condition can be diagnosed with certainty. Typically, the kidney is replaced by an irregular mass of grape-like cysts, which distort the normal reniform shape; no pelvis is visible, and the ureter is atretic, hypoplastic or malformed. By contrast, bilateral polycystic kidneys retain their reniform shape, because the myriads of cysts are more uniform in size; the pelvis and ureters are patent, convey urine and can be readily identified.

The renal parenchyma of R.W. had been almost completely replaced by cysts, the origin of which could not be determined with certainty, though their roundness suggests that they may be derived from glomeruli. No transitional cystic forms of glomerular capsules or tubules (Bialestock, 1956, 1958, 1959) were seen.

Dissection of the small nubbin of renal tissue revealed some nephrons of almost normal dimensions, and other nephrons showed the apposed thinned blind ends of both the distal convoluted tubules and the first collecting tubules (Figures III and IV). This is the first recorded occasion on which this abnormality—definite non-union of the excretory and collecting systems—has been observed by the micro-dissection technique.

Bremer (1957), in discussing the formation of cysts of the kidney, reiterates the current embryological theory, which is that the human kidney is formed from the metanephros, that union occurs between the excretory and collecting duct systems, that this union is situated at the junction of distal convoluted tubules with the first collecting tubules, and that cyst formation results from failure of union of these two components. The findings of non-union of the excretory and collecting systems are so typical in this child, and similar to those described by the embryologists, that non-union must be the explanation of this local deformity, but not necessarily of the cyst formation.

In contrast, microdissection study of the polycystic kidney in infancy (Bialestock, 1956) showed the nephrons to be all abnormal; bizarre transitional cystic forms involving glomeruli and any part of the tubules, as well as curious giant nephrons, were seen. It was postulated that abnormal stimuli would have been active very early in development of the kidney before normal differentiation had

occurred, and that failure of union of excretory collecting duct systems was not concerned. Whilst this failure of union accounts for some of the changes in the present tissue, the simple round cysts and the abnormalities of the ureter and the pelvis are not explained.

Potter (1952) has stated that there seems to be no justification for attempting to explain all polycystic kidneys (using the term generally for all cystic conditions in the kidney) on the same basis, and there appears to be little doubt that part or all of any kidney may be arrested at any stage of its development, or " that it may be secondarily disturbed after it has become normally differentiated ". The present findings are in accord with this, and the presence of normal nephrons, the simple round cysts and the abnormalities of the ureter and pelvis all suggest that stimuli acting on the developing embryo caused changes only after the kidney had already developed normally.

Since microdissection in the present case has shown appearances quite different from those of polycystic disease, it would seem that the morphogenesis of unilateral cystic disease in infancy should be regarded as different from that of polycystic disease. Clinically, such a differentiation has been suggested by all the other reports of unilateral multicystic kidney.

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SERUM COMPLEMENT LEVELS IN SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER DISEASES[1]

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SUMMARY

Serum hæmolytic complement has been measured in 166 patients. Low levels of complement occurred in systemic lupus erythematosus, in the nephrotic syndrome, and in parenchymal liver damage. High levels of complement occurred in obstructive jaundice and in conditions characterized by tissue destruction. The low serum complement level in systemic lupus erythematosus was attributed to complement-fixing antibodies against human tissues found in that condition.

IN the present study, serum complement has been measured in 166 patients suffering from diseases in which auto-immune mechanisms may play a part, such as systemic lupus erythematosus (S.L.E.), Hashimoto's thyroiditis, the nephrotic syndrome and rheumatoid arthritis, and also from liver disease, since the liver is believed to produce complement.

The finding of low serum complement levels in auto-immune disease is of interest, because many antibodies bind complement when they combine with their corresponding antigen. Hence a low serum complement level provides presumptive evidence for the occurrence of complement-fixing antibody-antigen reactions *in vivo*.

MATERIALS AND METHODS

Serum Complement Estimation

The method of Walton and Ellis (1958) was followed with minor modifications. Blood was allowed to clot at room temperature and kept at 4° C. until separated. Serum was separated within six hours and stored at —20° C. for not longer than 14 days. Lyophilized normal human serum was used as a control in each experiment. Sheep cells were collected weekly in Rous and Turner's solution (3·8% sodium citrate and 5·4% glucose in distilled water). Commonwealth Serum Laboratory rabbit anti-sheep hæmolysin was employed. All dilutions were made in calcium magnesium saline solution (Gajdusek. 1958). The sheep cells were washed three times and made up accurately to 6%. The cells were sensitized by adding an equal volume of calcium magnesium saline solution containing hæmolysin so as to give a final concentration of six minimal hæmolytic doses of antibody in 0·5 ml. of red-cell suspension. incubated for half an hour and kept at 4° C. The test serum was diluted 1 : 9 and distributed in dilutions from 1 : 9 to 1 : 59 in six tubes in a volume of 0·5 ml. One millilitre of calcium magnesium saline solution and 0·5 ml. of sensitized cells were added, and the tubes were incubated in a water-bath at 37° C. for one hour, being shaken at the half hour. The tubes were stored overnight at 4° C. The hæmoglobin in the clear supernatant was estimated colorimetrically without previous centrifugation. The colorimeter was calibrated with known dilutions of hæmolysed sheep blood. In no case was serum sufficiently jaundiced to interfere with the hæmoglobin estimation.

The serum dilution causing 50% hæmolysis was obtained by plotting the probit of the percentage hæmolysis against the reciprocal of the serum dilution. This figure was corrected to allow for the variation in the behaviour of the sensitized sheep cells in different experiments by dividing by the value for the lyophilized control. The mean reciprocal of the dilution of the lyophilized control, causing 50% hæmolysis in 13 experiments, was 30·8 with a standard deviation of 3·9. The average corrected value for the serum complement of 40 control sera from blood bank donors was 1·16. Because the corrected value is a ratio, it is convenient and permissible to divide it by 0·0116, and all results have been expressed in this form. With this adjustment, the mean normal value for the serum complement of 40 blood donors was 100 with a standard deviation of 14·8.

Complement Fixation

The auto-immune complement fixation (A.I.C.F.) test, which detects circulating complement-fixing antibodies against human tissue antigens, was performed as described by Gajdusek (1958). The same method of complement fixation, using both inactivated and uninactivated serum, was employed in an attempt to detect antibodies against denatured gamma globulin. The denatured gamma globulin was prepared by diluting Commonwealth Serum Laboratory human gamma globulin (160 mg. per millilitre) 1 : 9 and heating at 63° C. for 10 minutes.

Clinical Pathology Methods

The two-hour clot method of Magath and Winkle (1952) was used for the L.E. cell test. The method of Alexander and de Forest (1954) was employed for the Rose-Waaler test (Rose *et alii*, 1948). The F II test for the rheumatoid factor (Jacobson *et alii*, 1956) was performed by coating group O rhesus-negative human erythrocytes with denatured gamma globulin, using the tanned-cell technique of Fisher (1952).

[1] Received on July 13, 1959.

[2] Associate Assistant to the Clinical Research Unit, in receipt of a British Memorial Foundation Fellowship.

RESULTS

The sera from 40 blood donors were used to obtain normal values for serum complement. The average serum complement level of the blood donors was 100. The standard deviation was 14·8, giving a normal range for serum complement of 70 to 130. Table I summarizes the observations on 166 patients. Subnormal values occurred in S.L.E., Hashimoto's thyroiditis, the nephrotic syndrome and parenchymal liver disease. Values higher than normal were found in obstructive jaundice and in conditions characterized by tissue destruction such as ulcerative colitis.

TABLE I

Serum Complement Levels in Various Diseases

Disease	Number of Patients	Serum Complement Level		
		High	Normal	Low
Systemic lupus erythematosus	12	0	4	8
Conditions related to systemic lupus erythematosus	5	0	5	0
Hashimoto's thyroiditis	2	0	1	1
Nephrotic syndrome	6	1	3	2
Rheumatoid arthritis	13	3	9	1
Liver disease:				
Nutritional cirrhosis	9	0	2	7
Cirrhosis of unknown ætiology	8	0	5	3
Hæmochromatosis	5	1[1]	2	2
Infectious hepatitis	4	0	1	3
Obstructive jaundice	7	5	2	0
Chlorpromazine jaundice	1	1	0	0
Alcoholism	11	3[1]	7	1
Sarcoidosis	3	1	2	0
Ulcerative colitis	7	2	4	1
Miscellaneous conditions	73	6	62	5

[1] These patients had severe associated disease.

Complement Levels in Specific Diseases

Systemic Lupus Erythematosus (12 Cases).—All the patients had a clinical history suggestive of S.L.E., and the L.E. cell test produced a positive result at some stage of the illness. Nine of the patients were receiving cortisone and eight were in remission. Table II shows the serum level of complement in this group. The sera of eight of the 12 patients had subnormal complement levels. Five of these eight sera gave a positive response to the A.I.C.F. test, indicating the presence of circulating complement-fixing antibodies against human tissues, and an additional two patients were known to have given a positive response to the A.I.C.F. test previously. One of the four patients with normal serum complement had given a positive response to the A.I.C.F. test at the time when the serum complement level was measured; three of these four patients had previously given a positive response to the A.I.C.F. test. There was a tendency for low serum levels of complement to be associated with activity of the disease process and a positive result to the L.E. cell test (Table II).

Conditions Related to Systemic Lupus Erythematosus (5 Cases).—Table III gives the details of five patients who presented some of the features of S.L.E. One of these had rheumatoid arthritis and gave a positive response to the L.E. cell test; the second patient had polyarthritis, hepatosplenomegaly and thyroid enlargement, and gave a positive response to the L.E. cell test. At the post-mortem examination, a lymphosarcoma was found. The third patient presented with chronic discoid lupus and a past history of polyarthritis and purpura, and gave a negative response to the L.E. cell test. Two patients had lupoid hepatitis (Mackay *et alii*, 1959) and both had previously reacted positively to the L.E. cell test. All these patients had a normal serum complement level. One of the patients with lupoid hepatitis gave a strongly positive response to the A.I.C.F. test.

TABLE II

Serum Complement Levels in Systemic Lupus Erythematosus

Patient	Concurrent L.E. Test	A.I.C.F.[1]		Current Cortisone Therapy	Clinical Activity	Serum Complement
		Maximum	Present			
L.R.	−	N.A.	−	+	+	0
J.G.	−	++	++	+	−	21
D.	+	N.A.	++	−	+	32
M.W.	−	++	+	+	−	45
L.A.	+	N.A.	++	+	−	53
P.W.	−	+	−	+	−	55
B.	−	N.A.	++	−	+	58
S.I.	+	++	−	+	−	69
O.K.	−	++	++	−	+	74
R.M.	−	+	−	+	−	76
B.B.	−	+	−	+	−	87
R.G.	−	−	−	+	−	87

[1] A.I.C.F., auto-immune complement fixation test; " − " implies a titre of less than $\frac{1}{4}$ to liver and kidney; " + " implies a titre of $\frac{1}{4}$ or $\frac{1}{8}$; " ++ " implies a titre of $\frac{1}{8}$ or greater; " N.A." means that no data are available.

TABLE III

Serum Complement Levels in Conditions Related to Systemic Lupus Erythematosus

Patient	L.E. Cell Test		A.I.C.F.[1]		Clinical Features	Serum Complement
	Past	Present	Maximum	Present		
T.H.	–	+	N.A.	–	Rheumatoid arthritis	116
A.F.	N.A.	+	N.A.	–	Polyarthritis. Liver, spleen, thyroid enlarged. Leucocytosis. Lymphosarcoma at autopsy	81
O'L.	N.A.	–	N.A.	–	Chronic discoid lupus. Previous polyarthritis and purpura	111
T.I.	+	–	–	–	Cirrhosis of the liver. Previous polyarthritis and ulcerative colitis	110
M.A.	+	–	++	++	Cirrhosis of the liver. Previous polyarthritis	108

[1] See footnote to Table II.

Hashimoto's Thyroiditis (*2 Cases*).—The diagnosis was established histologically, and complement-fixing antibodies to crude thyroid extract were demonstrated in both patients. One patient, who was also suffering from cirrhosis of the liver, had normal serum complement levels. The other patient, L.C., was of particular interest, because her serum complement level was persistently low and often absent, and was unaffected by treatment with cortisone.

L.C., a married woman, aged 54 years, presented herself in 1950 with a 20 years' history of classical deforming rheumatoid arthritis. In 1953 she developed sclerosing thyroiditis, and partial thyroidectomy was undertaken. In 1959 she developed œdema of the glottis, which required tracheotomy. During treatment with cortisone, the attacks of laryngeal œdema ceased. A persistent eosinophil count of 14,000 per cubic millimetre was uninfluenced by cortisone. The complement-fixing antibody titre to crude thyroid extract was 1/32. The Rose-Waaler test for rheumatoid arthritis produced a negative response.

Nephrotic Syndrome (*6 Cases*).—Six patients with the nephrotic syndrome presumably due to glomerulonephritis were studied. Low serum values of complement were found in two patients, and high values in two patients. One additional patient in whom the nephrotic syndrome was due to S.L.E. (*vide supra*) had a low serum complement level. Ellis and Walton (1958) made similar observations.

Rheumatoid Arthritis (*13 Cases*).—Nine patients had normal serum complement levels; six were receiving cortisone. Three patients had elevated serum complement levels; none were receiving cortisone. One patient suffering from his second acute attack of rheumatoid arthritis had a low serum complement level. Table IV summarizes these findings.

The normal serum complement level in most patients with rheumatoid arthritis was in contrast to the low levels found in S.L.E. This led to the observation that the rheumatoid factor did not behave like a complement-fixing antibody. Six rheumatoid arthritis sera giving strong agglutination of cells coated with denatured gamma globulin in the F II test were tested for the presence of complement-fixing antibodies against human gamma globulin denatured by heating. No complement-fixing antibodies were detected.

TABLE IV

Serum Complement Levels in Rheumatoid Arthritis

Patient	Current Cortisone Therapy	Deformity	Clinical Activity	Serum Complement Level
H.E.	–	++	++	146
D.O.	–	+	++	138
C.H.	–	–	++	130
S.P.	–	++	++	124
W.H.	–	+	–	103
T.H.	–	++	–	95
H.E.	–	–	++	54
W.A.	+	++	+	108
M.K.	+	+	+	105
D.R.	+	++	+	101
C.A.	+	++	++	100
S.E.	+	+	+	87
B.R.	+	+	+	86

Liver Disease.—Fifteen of the 26 patients with parenchymal liver damage had a subnormal serum complement level. Five of the seven patients with obstructive jaundice had elevated serum complement levels.

Seventeen patients with cirrhosis of the liver were studied. Ten had a subnormal serum complement level; in four the serum complement level was below 60. There was no clear-cut correlation between the serum complement level on the one hand and the clinical activity and results of biochemical tests on the other. One patient with a normal serum complement level gave a strongly positive response to the A.I.C.F. test. Similar findings

were obtained by Dulaney (1948), by Jordan (1953) and by Mandel and Lange (1955).

Out of five patients with hæmochromatosis, two had subnormal serum complement levels. One patient with an associated carcinoma of the lung had a high serum complement level.

Four patients with infectious hepatitis were studied. Two out of three patients had low serum complement levels in the first 14 days of their clinical illness, at a time when they were jaundiced. A fourth patient with non-resolving acute infectious hepatitis had a low serum complement level. Normal serum complement levels were found in four patients who had recovered from infectious hepatitis.

Five out of seven patients with obstructive jaundice due to extrahepatic biliary obstruction had highly elevated serum complement levels. Of the two patients with normal serum complement levels, one had a mild transient obstruction from a gall-stone in the common bile duct, and the other had complete obstruction for three months from a carcinoma of the head of the pancreas.

One woman with chlorpromazine jaundice and biochemical findings suggestive of obstructive jaundice had a high serum complement level. The serum complement level was normal in two patients who had recovered from chlorpromazine jaundice.

Eleven alcoholic patients with no clinical or biochemical evidence of liver damage were studied. Seven had normal serum complement levels. Two with recently fractured ribs, complicated in one case by a hæmothorax, had high serum complement levels. One with associated myocarditis had a transiently elevated serum complement level. One had a low serum complement level.

Sarcoidosis (3 Cases).—One patient with acute sarcoidosis involving the liver and spleen had a high serum complement level. A patient with miliary lung shadows had a normal serum complement level while taking cortisone, which dropped below the normal range when cortisone was stopped. The third patient with inactive sarcoidosis involving the carpal phalanges had a normal serum complement level.

Ulcerative Colitis (7 Cases).—Two patients with active ulcerative colitis had raised serum complement levels; one of these gave a positive response to the A.I.C.F. test. One patient with mild ulcerative colitis had a low serum complement level. Four patients had normal serum complement levels.

Miscellaneous Conditions (73 Cases).—Six patients had high serum complement levels. In five, considerable tissue destruction was occurring. Their diagnoses were, respectively, Crohn's disease with fistula formation, acute pancreatitis, carcinoma of the prostate with bony metastases, acute lymphatic leukæmia and myocardial infarction. The sixth patient had a hæmatemesis from a duodenal ulcer. Four other patients with myocardial infarction and one with acute myeloid leukæmia had normal serum complement levels.

Five patients had low serum complement levels. One patient was suffering from an obscure lipogranulomatous condition. His serum albumin content was 2·0 grammes per 100 ml. and his serum gamma globulin content 1·9 grammes per 100 ml. The other patients were suffering from Coombs-positive acquired hæmolytic anæmia, myelofibrosis and steatorrhœa; the fifth patient was apparently healthy, but had presented with symptoms compatible with resolving nephritis. Another patient with steatorrhœa from Whipple's disease had normal serum complement levels. Reader (1955) found low serum complement levels in patients with acquired hæmolytic anæmia.

Inhibitors of Serum Complement

Cushman *et alii* (1957) described a number of dialysable inhibitors of hæmolytic complement. To test for the presence of these factors in serum, the sera of two patients with high complement levels and of two patients with no complement were dialysed at 4° C. overnight against five volumes of calcium magnesium saline solution. The dialysing fluid was used as diluent for the estimation of the complement level of normal serum. No evidence of a dialysable factor influencing the serum complement level was obtained in these four cases.

DISCUSSION

Complement was originally described by Bordet (1895, 1898) as a heat-labile factor necessary for the lysis of *Vibrio choleræ* and red cells by their corresponding antisera. Bordet and Gengon (1901) demonstrated that many antibodies bound complement in the presence of their corresponding antigen. It was subsequently found that complement was composed of four components which are necessary for the lysis of sensitized red cells. The present views of the enzymic nature of the components of complement are summarized by Becker (1958).

The liver may manufacture at least some of the components of complement. Low complement levels in animals in which the liver has been ablated (Gordon, 1955) or damaged by poisons such as ethionine (Rice, 1954) and in

humans with parenchymal liver disease are compatible with this view.

The present finding of low serum complement levels in S.L.E., the nephrotic syndrome and parenchymal liver disease, and of high serum complement levels in obstructive jaundice and tissue destruction, is in keeping with other reports on complement levels in the recent literature.

A low serum complement level was found in eight out of 12 patients with S.L.E. Similar findings were reported by Elliott and Mathieson (1953), by Wedgewood and Janeway (1953) and by Williams and Law (1958). Williams and Law, in a series of 58 cases, were able to correlate the finding of low serum complement levels with clinical activity. In five of the eight patients in the present series with low serum complement levels, circulating complement-fixing antibody against human and animal tissues was demonstrated, and the lowered serum complement level was therefore attributed to the reaction of these antibodies with human tissue antigens *in vivo*.

The failure in some cases to detect complement-fixing antibody, the presence of which was suggested by the finding of low serum complement levels may be due to (*a*) the absorption of the antibody *in vivo*, (*b*) the presence of soluble antigen-antibody complexes, or (*c*) the failure to test with the appropriate antigen.

The occurrence of normal or high serum complement levels in patients with circulating complement-fixing antibodies against human tissues may be related to the opposing effects of complement-fixing antibody-antigen combination and tissue destruction on the serum complement level. Thus, Fischel and Gajdusek (1952) observed that, although a low serum complement level was an almost invariable finding in acute nephritis, normal levels occurred when acute nephritis was complicated by conditions known to be associated with a raised serum complement level.

Normal serum complement levels were found in nine out of 13 patients with rheumatoid arthritis. Because most of these patients were receiving cortisone, these figures are not comparable with those of Vaughan *et alii* (1951) and of Williams and Law (1958), who found elevated serum complement levels in rheumatoid arthritis which returned towards normal during treatment with cortisone, or with those of Kellett (1954), who found normal values in the majority of untreated patients.

The finding of high or normal serum complement values in rheumatoid arthritis is not against the view that rheumatoid arthritis is an auto-immune disease, as the rheumatoid factor, which behaves like an antibody against gamma globulin, does not bind complement in the presence of its antigen.

The high serum complement levels observed in obstructive jaundice were also found by Dulaney (1948), by Jordan (1953) and by Mandel and Lange (1955). Fischel (1953) and Boltax and Fischel (1956) described raised serum complement levels in tissue destruction. It is not known whether the raised serum complement level in disease is due to a true rise in the serum complement level, from either increased production or reduced destruction, or to factors other than the four components of complement such as the carbohydrases described by Leroy and Spurrier (1955), which occur in normal tissues and are particularly active in lysing sensitized cells.

Serum complement estimation is a feasible procedure in a routine laboratory, and there are a few situations in which it is of help in establishing a diagnosis. Ellis and Walton (1958) have pointed out that, whereas low serum complement levels are a consistent finding in acute nephritis, levels are normal in chronic nephritis and in malignant hypertension. Serum complement estimation may thus be of real value in the diagnosis of acute nephritis. The finding of a low serum complement level strengthens the diagnosis of systemic lupus erythematosus, but the finding of a normal serum complement level does not exclude it. In hæmolytic anæmia the finding of a low serum complement level suggests an immunological mechanism of red cell destruction (Reader, 1955). Jordan (1953) found that serum complement estimation was useful in distinguishing obstructive and hepato-cellular jaundice. None of the patients in the present series with parenchymal liver damage had raised serum complement levels.

The real interest in serum complement lies in the evidence that it provides for the occurrence of antibody-antigen combination *in vivo*. When low serum complement level and complement-fixing antibodies against human tissue occur in patients with S.L.E., there is good evidence that tissue damage is due to auto-immune processes. Furthermore, these findings shed light on the problem of whether the mechanism of tissue damage in S.L.E. is analogous to immediate or delayed hypersensitivity.

In immediate hypersensitivity such as anaphylactic shock and serum sickness, tissue damage is due to circulating antibody or circulating antigen - antibody complexes (Germuth and McKinnon, 1957); infiltration

of the lesions with inflammatory cells is secondary to tissue damage, and the serum complement level is usually low (Schwab *et alii*, 1950). In delayed hypersensitivity, such as the homograft rejection reaction, circulating antibody is unimportant and may be absent; cell infiltration is primary, and is responsible for the tissue damage seen (Lawrence, 1956). The serum complement level is normal or raised (Favour *et alii*, 1953).

The pronounced cellular infiltration of the liver in lupoid hepatitis and of other sites in S.L.E. may be primary, and analogous to that seen in delayed hypersensitivity. On the other hand, the focal necrosis, basement membrane thickening and obliteration of the glomerular tufts in the kidney in S.L.E. usually occur in the absence of significant cellular infiltration (Joske and Stubbe, 1957; Pollak *et alii*, 1958). This suggests that tissue damage is not due to local concentration of antibody-producing cells, but to humoral factors such as circulating antibody or antigen-antibody complexes.

The tissue damage may be due to antibody directed against the glomeruli. On the other hand, the occurrence of circulating antibody against soluble tissue antigens (Asherson, 1959) produces a situation qualitatively similar to serum sickness. In serum sickness, the occurrence of antibody and soluble antigen in the circulation is the prerequisite of tissue damage. As glomerular damage is seen in both S.L.E. and experimental serum sickness (Rich, 1956), these findings support the view of Rich and Gregory (1947) that some of the manifestations of S.L.E. are analogous to those seen in experimental serum sickness.

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THE USE OF AN ALDOSTERONE ANTAGONIST IN PATIENTS WITH CIRRHOSIS[1]

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SUMMARY

The steroidal spirolactone SC 8109, an aldosterone antagonist, was used in two cases of hepatic disease and ascites resistant to ordinary medical treatment. In both cases there was an increased sodium excretion in the urine, while one of the patients had a significant weight loss and a reduction of her ascites. This substance should prove useful in the further evaluation of aldosterone in the pathogenesis of fluid retention in œdematous states, and possibly in their treatment.

THE isolation by Simpson *et alii* (1952) of a potent sodium-retaining factor (later termed aldosterone) from adrenal venous blood was followed rapidly by the demonstration of this hormone in increased amounts in the urine of patients with nephrosis (Luetscher *et alii*, 1954), congestive cardiac failure (Luetscher *et alii*, 1956) and ascites due to cirrhosis (Luetscher and Johnson, 1954; Axelrad *et alii*, 1955; Wolff and Koczorek, 1955). The part which aldosterone plays in the pathogenesis of fluid and salt retention in these diseases varies from patient to patient, and even in the same person it depends on the stage of the disease and the therapy in use at the time.

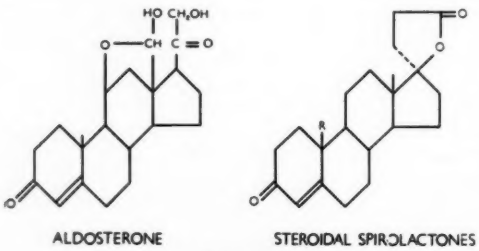

FIGURE I

The chemical formulæ of aldosterone and the steroidal spirolactones; in SC 8109 R=H, and in SC 5233 R=CH_3

Assessment of the significance of the hormone has been hampered by considerable difficulty in its quantitative determination, but recently two compounds have been synthesized which appear to have specific anti-aldosterone activity; they are the steroid-17-spirolactones SC 8109 and SC 5233 (Figure I). The present report concerns the use of the first and more potent of these substances[1] in two cases of hepatic disease and ascites resistant to ordinary therapy.

CLINICAL INVESTIGATION

Patient I, a woman, aged 56 years, had developed recurrent attacks of jaundice and right-sided hypochondrial discomfort after a cholecystectomy nine years previously; she had been unrelieved by surgical exploration of the common bile duct five years later. For the 12 months prior to this investigation she had required a paracentesis abdominis every four weeks, and approximately six litres of ascitic fluid were removed on each occasion. Her ascites was unresponsive to dietary salt restriction and to chlorothiazide, though there was a very small increase in urinary output after "Mersalyl" had been given. She was considered, on clinical grounds, to have biliary cirrhosis, though the diagnosis had not been confirmed by liver biopsy. At the time of the study the biochemical findings in her serum were as follows: bilirubin content, 1·2 mg. per 100 ml.; alkaline phosphatase, 46 King-Armstrong units; thymol flocculation, "++++"; zinc sulphate turbidity, 15 units (normal, <9 units). The serum electrolytes were within normal limits.

Patient II, a woman, aged 38 years, had 16 years' history of dyspnœa, followed later by ankle swelling and abdominal distension. A clinical diagnosis of constrictive pericarditis was made at the age of 32 years, but this was disproved at thoracotomy, when she was found to be suffering from non-specific cardiomyopathy; a liver biopsy at that time revealed the appearances of cardiac cirrhosis. For several years prior to this study, rapid reaccumulation of ascites had been her principal problem, and she had

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[1] Supplies of the steroidal spirolactone SC 8109 were generously made available by Messrs. G. D. Searle & Co., Chicago, U.S.A. One millilitre of the supplied solution contained 100 mg. of SC 8109 in a mixture of propylene glycol (50%), benzyl alcohol (20%) and distilled water (30%).

required paracentesis with the removal of approximately seven litres every five weeks. The ascites had been resistant to dietary salt restriction, mercurial diuretics and chlorothiazide. At the time of this investigation, the serum biochemical findings were as follows: bilirubin content, 0·6 mg. per 100 ml.; alkaline phosphatase, 12 King-Armstrong units; thymol flocculation, "+"; zinc sulphate turbidity, nine units; sodium content, 130 mEq/l.; potassium content, 3·6 mEq/l.; chloride content, 99 mEq/l.; bicarbonate content, 23 mEq/l.; protein content, 7·6 grammes per 100 ml. (albumin, 5·1 grammes per 100 ml.). The bromsulphalein retention was 20% in 45 minutes.

Both patients were studied in a metabolic ward. They were weighed daily under standard conditions, and the urinary volume and sodium, potassium and chloride contents were measured. Serum electrolyte and liver function tests were performed regularly. Fluid intake was unrestricted. Throughout the whole investigation, both patients received one gramme of chlorothiazide and 45 mEq of potassium supplement per day, while Patient II was also treated with 1 mg. of digoxin per day.

Patient I was given a diet calculated to contain a constant 40 mEq of sodium per day. She received two courses of the steroidal spirolactone SC 8109 by intramuscular injection, the first of 0·5 gramme in two doses four hours apart, and the second of 1·5 grammes in six doses over 48 hours. Patient II received two identical courses of SC 8109, each of 1·5 grammes in six doses over 48 hours; the first was given while she was taking a diet containing 80 mEq of sodium per day, and the second when the dietary sodium intake was 40 mEq per day.

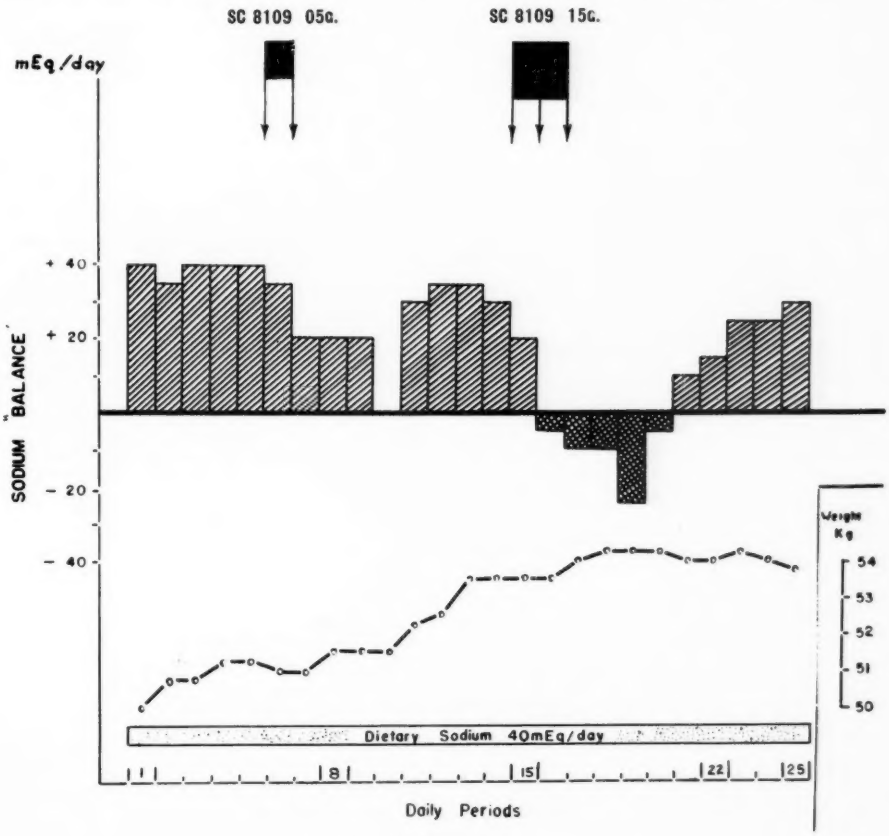

FIGURE II

Patient I: The effect of SC 8109 on sodium balance and body weight

RESULTS

The sodium balances of the two patients are shown in Figures II and III respectively; the difference between calculated intake and measured urinary excretion has been plotted so that a positive balance (i.e., sodium retention) has been drawn upwards from the base line and a negative balance downwards. Sodium losses from sweat and stools have been neglected, but there was no reason to assume that these

changed significantly during the studies. There are no figures available for sodium balance on the tenth day of the study for Patient I, and on the twenty-first day for Patient II, as urine collections were incomplete on these days.

In Patient I, the smaller dose of SC 8109 (0·5 gramme) produced a slight increase in urinary sodium excretion, but the over-all balance remained positive. The larger dose (1·5 gramme) had a more marked natriuretic effect, which was maximal on the third day after completion of the course, and lasted for about a week; she was in negative balance for a total of five days. Though the daily urinary volume was not significantly altered, there appeared to be a temporary halting of weight gain in the period after SC 8109 therapy (due to decreased oral fluid intake); the abdominal girth was constant.

In Patient II the first course of SC 8109, given while she was taking a diet containing 80 mEq of sodium per day, produced a marked increase in urinary sodium excretion, and the predominantly negative sodium balance persisted for 10 days after the last injection of the drug. The same dose of SC 8109 while she was having a diet containing 40 mEq of sodium per day caused approximately the same result. The urinary volume did not alter greatly with either course, but she lost weight on both occasions, and there was a clinically evident small diminution of abdominal girth.

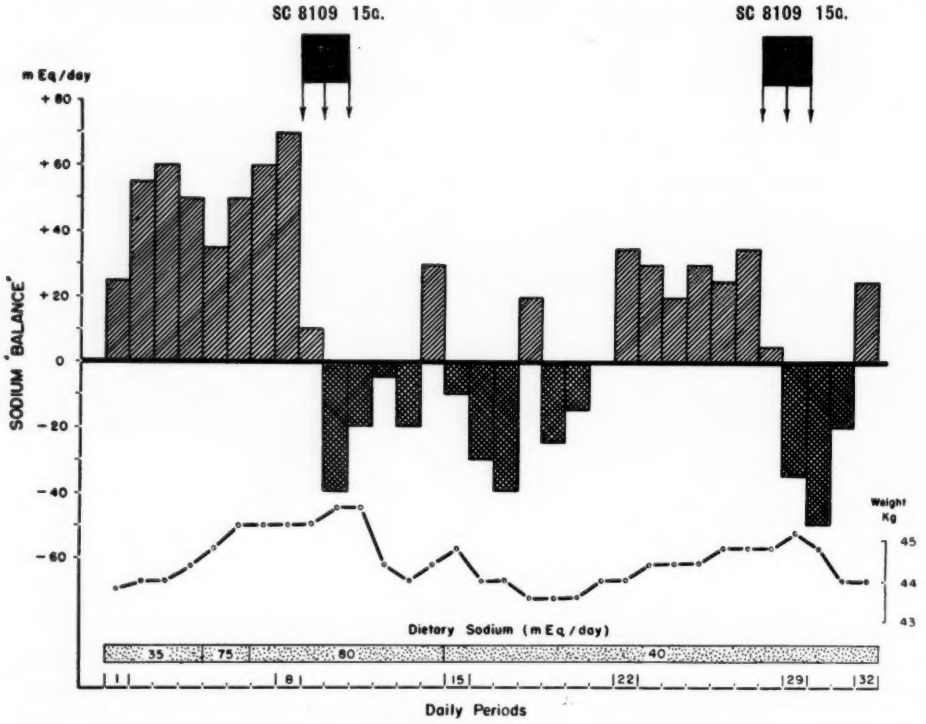

FIGURE III

Patient II: The effect of SC 8109 on sodium balance and body weight

In neither patient was there any significant change in the serum electrolyte concentrations or the results of liver function tests during the investigation; there was no alteration in urinary potassium excretion. No toxic manifestations of the drug were noted.

DISCUSSION

The accumulation of ascites in patients with cirrhosis of the liver has been attributed in the first place to local factors such as portal hypertension and blockage of hepatic lymph drainage, assisted in some cases by hypoalbuminæmia; the over-all fluid and salt retention by the kidneys may be related to decreased hepatic inactivation of antidiuretic hormone, aldosterone

and other adreno-cortical hormones, as well as to increased aldosterone production secondary to the tendency towards a diminished circulating blood volume. The actual, rather than the theoretical, pathogenetic significance of secondary hyperaldosteronism has been doubted, especially since fluid retention has been singularly rare in reported cases of primary aldosterone-secreting adrenal adenomata, in which the classical disturbances have been hypertension and marked hypokalæmic alkalosis.

Nevertheless, in the attempt to reduce aldosterone production in cirrhotics with ascites, bilateral adrenalectomy has been performed in a small number of cases with limited success (Marson, 1954; Giuseffi *et alii*, 1957). Another approach has been the use of amphenone B, which inhibits adrenal synthesis of all corticosteroids, but particularly aldosterone (Hertz *et alii*, 1956; Thorn *et alii*, 1956; Renold *et alii*, 1957). The experience of Summerskill and Crabbé (1957) with this drug was that it caused marked diuresis and urinary sodium loss in two patients with "resistant" ascites, but that it had little effect in two other subjects whose ascites was responsive to dietary sodium restriction, bed rest and mercurial diuretics; however, in all four subjects there was a pronounced fall in the urinary aldosterone excretion. The quite marked toxic effects of amphenone, its limited availability, and the requirement of concurrent cortisone or prednisone supplements have precluded its therapeutic use except in exceptional circumstances.

The two recently synthesized steroidal spirolactones apparently act by antagonizing the peripheral action of aldosterone (and to a lesser extent desoxycorticosterone), and there is no inhibition of the functions of other corticosteroids; there is no effect on adrenal synthesis. It has been shown that they have no action on adrenalectomized dogs and rats, or on patients with Addison's disease not receiving replacement therapy; they suppress the sodium-retaining and potassium-losing effects of injected aldosterone or desoxycorticosterone acetate (Kagawa *et alii*, 1957; Liddle, 1957, 1958). Both drugs have been used in the treatment of patients with congestive cardiac failure and nephrosis, some clinical improvement being noted (Liddle, 1958). Kerr and his co-workers (1958) gave SC 8109 (the substance used in the present study) to three subjects with resistant ascites; two of these had an increased urinary sodium excretion (in only one case did this exceed intake), whereas the third patient showed no response at all. In none of the three was a significant weight loss recorded.

The fact that both our patients had a natriuretic response to SC 8109 is evidence that aldosterone was playing a part in the maintenance of their ascites. However, it is clear that this was not the major factor causing fluid retention in Patient I, since the relatively large dose of 1·5 gramme over two days did not cause any weight loss or diminution of her ascites. This dose is probably over 1000 times the amount of aldosterone synthesized daily in cases of hyperaldosteronism; the need for such a large quantity to produce significant effect may be related to slow absorption from the intramuscular site, as well as to local inactivation; Liddle (1958) has demonstrated a much more rapid effect following oral rather than parenteral administration of SC 8109.

It is of interest in relation to Patient II that the same course of aldosterone, on sodium intakes of 80 and 40 mEq per day respectively, had very similar effects on her overall sodium balance and body weight. This suggests that aldosterone production had not been significantly depressed by the higher sodium content of the diet, a finding contrary to the experience of most workers (Luetscher and Curtis, 1955; Duncan *et alii*, 1956).

It is apparent from these limited investigations that there are considerable opportunities for further studies with SC 8109 in the evaluation of aldosterone in the pathogenesis of ascites as well as other œdematous states. It would be valuable to use the drug in a variety of diseases with varying sodium and potassium dietary intakes, and in association with changing diuretic régimes. Results are obtained much more simply than by the estimation of urine and plasma aldosterone concentrations, or by calculation by means of the tritium-labelled derivative (Ayres *et alii*, 1958) of the total amount of the hormone produced daily. These latter methods are difficult, and in the case of the urinary aldosterone excretion, interpretation is complicated by the probability that the human kidney does not always handle this hormone in the same way.

Unfortunately the synthesis of SC 8109 is expensive and is not yet a commercial proposition, so the amount available for investigative purposes is still very limited. Should the situation change, its relative lack of side effects may well encourage its use in the therapy of many patients with resistant œdema.

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performing the biochemical determinations, and Mr. K. Clifford, Department of Illustration, University of Sydney, for assistance with the diagrams.

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A Review Written by Request

THE CONCEPT OF A VOLUME RECEPTOR[1]

T. E. Lowe
From the Baker Medical Research Institute, Melbourne

Regulation of the total volume of fluid within the body is one aspect of homœostasis, and in the mature individual it is within very narrow limits. Although recognition of the stability of this volume in normal individuals has been accepted for a long time (Henderson, 1916), the mechanism by which this regulation is accomplished has not been established with any completeness.

Body fluids are mainly solutions of electrolytes in water as a solvent, and the volume of water is vastly greater than that of the solutes. Volume regulation must therefore be primarily a regulation of the volume of water in the body. This situation leads to one difficulty which many investigators have encountered, and which is referred to by Wolf (1958) as " the conceptual difficulty of distinguishing the effect of the mass of salt and water of a load of saline from the distortion of volume produced by the load ". Furthermore, consideration of the volume of water in the body cannot be entirely divorced from the regulation of the concentration of the solutes, the regulation of body temperature and, in the immature individual, the regulation of growth.

Analogy with other mechanisms of physiological regulation suggests that there will be somewhere in the body a structure or structures which can monitor body fluid volume. This concept of a " volume receptor " seems to have been first discussed by Peters (1935), and since then many workers have sought evidence for the site and nature of such a structure or structures, or have considered that the data concerning the metabolism of water require the postulation of such a receptor (McLean, 1925 ; Lowe and Sayers, 1952).

So far no " volume receptor " has been localized, and in any discussion on this concept it will be necessary to examine, first, the evidence that a mechanism for volume regulation exists independently of the other mechanisms known to influence water content, secondly, the nature of that mechanism and its component parts and, thirdly, the predicted properties of the postulated receptor.

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Evidence for Volume Regulation

The constancy of the volume of water in the adult body is not direct evidence for the control of its volume, *per se*, for it is influenced by many mechanisms not concerned with volume. Variations in temperature, growth and control of osmotic pressure of the body fluids influence the water content of the body. To establish that volume regulation occurs independently of these other systems requires demonstration that, after the effects of those systems have been accounted for, there is separate control of the volume of water in the body.

A simple analogy is to regard the body as an " open " storage system, into which goes a continuous inflow of water, and from which leaves a continuous outflow. If, after the influence of the systems mentioned on the flow of water through this storage has been accounted for, it can be shown that the volume of water in the storage controls the inflow and outflow in such a manner as to counteract volume changes, then one must postulate that volume control, *per se*, exists.

Because of its considerable influence on the intake and outflow of fluid, it has been suggested from time to time, and again recently by Bresler (1956), that the control of osmotic pressure of the body fluids is adequate to control the volume of the body fluid. This suggestion, however, ignores the fact pointed out by Henderson (1916) that any given osmotic pressure can occur at any given volume provided the solute content is appropriately adjusted ; in other words, regulation of a ratio will not control the absolute value of either member of the ratio. Various investigations have shown that excesses or deficits in body-water volume are made good

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Analogy with other mechanisms of physiological regulation suggests that there will be somewhere in the body a structure or structures which can monitor body fluid volume. This concept of a " volume receptor " seems to have been first discussed by Peters (1935), and since then many workers have sought evidence for the site and nature of such a structure or structures, or have considered that the data concerning the metabolism of water require the postulation of such a receptor (McLean, 1925 ; Lowe and Sayers, 1952).

So far no " volume receptor " has been localized, and in any discussion on this concept it will be necessary to examine, first, the evidence that a mechanism for volume regulation exists independently of the other mechanisms known to influence water content, secondly, the nature of that mechanism and its component parts and, thirdly, the predicted properties of the postulated receptor.

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Evidence for Volume Regulation

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A simple analogy is to regard the body as an " open " storage system, into which goes a continuous inflow of water, and from which leaves a continuous outflow. If, after the influence of the systems mentioned on the flow of water through this storage has been accounted for, it can be shown that the volume of water in the storage controls the inflow and outflow in such a manner as to counteract volume changes, then one must postulate that volume control, *per se*, exists.

Because of its considerable influence on the intake and outflow of fluid, it has been suggested from time to time, and again recently by Bresler (1956), that the control of osmotic pressure of the body fluids is adequate to control the volume of the body fluid. This suggestion, however, ignores the fact pointed out by Henderson (1916) that any given osmotic pressure can occur at any given volume provided the solute content is appropriately adjusted ; in other words, regulation of a ratio will not control the absolute value of either member of the ratio. Various investigations have shown that excesses or deficits in body-water volume are made good

both in man and in animals by variation in either, or both, water intake and urine outflow (Adolph, 1950; Kanter, 1953; Cort, 1954). Clinical studies of patients recovering from œdematous conditions (Lowe, 1957) likewise show that both the intake and outflow of water are affected in a manner consistent with primary volume regulation. In these studies, the experimental conditions were such that the effects on water control resulting from metabolism, temperature regulation and osmotic pressure control could either be considered to be held constant or be recorded and accounted for.

Strauss *et alii* (1951), whilst studying the diuretic effect of expansion of extracellular fluid volume in normal volunteers, showed that such expansion produced a diuresis when the subject was recumbent, but not when he was sitting. Similarly, it has been observed (Lowe, 1958) that, during recovery from generalized œdema, œdema in dependent limbs often remains after other parts of the body have lost their excess fluid, and that this fluid can be excreted from the body if the limbs are elevated. It appears, therefore, that the distribution of excess fluid in the body can influence the body response.

In a series of observations, Adolph (1946, 1956) was able to show that, in acute water loading by mouth, the rate of urine flow was related to body weight. If body weight was taken as an index of body-fluid volume, this relationship showed a rapidly increasing rate of urine flow with a rising body-fluid volume. Further, over a very considerable range of flow rates the relationship was almost linear. Similar relationships in long-term observations of a normal subject and also in patients recovering from œdema have been recorded (Lowe, 1956). From these patients some evidence was obtained to suggest that the rate of fluid intake (thirst) is related to body-fluid volume in a manner reciprocal to that of urine flow.

These observations provide evidence that the volume of body water and intake and outflow of fluid are related in such a manner that they would form a system which is self-regulating for volume. These relationships are independent of other mechanisms in which water plays a part.

To account for the known facts, it is necessary, therefore, to postulate volume regulation of body water, and a self-regulating open system appears to be indicated. Such a system will require something which can monitor changes in volume and actuate the changes in the inflow and outflow mechanisms.

The Nature of the Control Mechanism

In the most general terms, the observation that the volume of body fluid regulates the intake of water (thirst) and its outflow (urine) can be explained by the assumption that both these flows are directly influenced by the fluid volume. There are, however, too many known components in the chain of regulation (see later) for this simple situation to be likely. Alternatively, there is some structure somewhere in the body which is sensitive to changing volume, and this structure provides the components of the inflow and outflow mechanisms with information. Such a structure is to be justly called a " volume receptor " (Welt and Orloff, 1951).

When the existence of a volume receptor is accepted, other questions arise: Where is it situated? How is it linked to the effector mechanisms?

Site of the Receptor

Many investigators have sought evidence to indicate which portion of the body fluid is monitored for volume. Peters (1952) considered that the metering of volume must be a function of some particular part of the circulation. Borst (1938, 1948) related cardiac output and renal excretion; Cort (1952), Judson *et alii* (1955) and Watson *et alii* (1955) related blood volume and renal excretion; Welt and his co-workers (1953) related plasma volume expansion with diuresis; and it has recently (Lowe, 1958) been shown in one case that the rate of urine flow was linearly related to plasma volume. Gregersen (1932) and Epstein (1953, 1955, quoted by Wolf, 1958) noted similar associations between thirst and vascular volume. None of these investigations has indicated just which portion of the vascular system is monitored for volume.

Harrison and his co-workers (1950, 1952, 1953), after studying the effect of posture and of compression of neck veins both in normal subjects and in patients with congestive cardiac failure, concluded that there was evidence for an intracranial site for a volume-regulating mechanism; but investigations by Bull (1953) and Fishman (1953) threw doubt on this interpretation.

A position in the venous side of the circulation within the thorax has been suggested by Drury *et alii* (1947), by Gauer *et alii* (1951, 1954) and by Sieker *et alii* (1954) for the volume receptor. These investigators have demonstrated a relationship between intrathoracic pressures and renal function.

With one exception (Lowe, 1956) these investigations concern responses in short-term experiments, and perhaps have little validity in relation to adjustments of body function to long-term disturbances.

Although the very simple analogy of the body as an open water-storage system has been mentioned, the fluid of the body is stored in many compartments separated by semi-permeable membranes, and the compartments can exchange water through the vascular system, which also serves to connect them with the organs of intake and outflow. The vascular system is therefore an integral part of the inflow and outflow mechanisms. In such a complex structure, it is unlikely that every compartment would be monitored for volume, and this would be unnecessary because the partition of fluid between compartments is controlled by the balance of a number of forces. Stability of these forces would maintain the relative volumes of fluid in the compartments, and monitoring of only one compartment would be adequate to monitor total volume. Local alterations in the balance of partitioning forces would produce local alterations in the volume of fluid. This occurs, for example, when a limb is kept in a dependent position for a length of time, as by splinting or prolonged sitting in an aircraft seat. Hypoproteinæmia may alter the partition ratios and also produce an upset in the total body water. Local alteration in the partitioning of fluid in unmonitored regions would explain the observation that the distribution of fluid influences the response of the body to water loads.

Effector Mechanisms

Information from the volume receptor must be conveyed to the inflow and outflow mechanisms. The inflow mechanism manifests itself as a conscious demand or revulsion for water intake. The desire for fluid is undoubtedly influenced by psychological factors—often it is almost a conditioned reflex (Wolf, 1958)—and it is a reaction to hyperosmolarity of body fluids (Gilman, 1937; Holmes and Gregersen. 1947); but more importantly for the present discussion, it is created by a lack of body-fluid volume (Gilman, 1937; Adolph, 1950).

The outflow mechanism is the kidney and the vascular system connecting the kidney with the various body compartments. Agents known to control the amount of urine formed are the pressure-flow pattern of blood in the nephrons, the composition of glomerular filtrate, and tubular activity which is acted on by the hormones, A.D.H. of the posterior putuitary lobe influencing water loss and aldosterone of the adrenal cortex influencing electrolyte loss. However, there is as yet no evidence that volume changes affect the amount of A.D.H. liberated by the pituitary, although it is clear that changes in osmotic pressure of the fluids can do so (Verney, 1946). There is some evidence that changes in fluid volume do influence the production of aldosterone (Bartter *et alii*, 1956); but this could influence fluid outflow only indirectly through osmotic pressure control arising from the aldosterone control of electrolyte loss. Again, no conclusive evidence exists to link changes in the pressure-flow pattern of fluid through the nephron with changes in body-fluid volume, although the close association of cardiac failure with disturbance of volume control possibly hints that this may be important (Bull, 1953).

Observations made by a number of investigators indicate that some portion of the nervous system takes part in the mechanisms regulating volume. Andersson and McCann (1955) demonstrated in the goat that stimulation of a region in the hypothalamus produced a drinking reaction, and in dogs (1956) they produced aposia by ablation of this "drinking area". Kourilsky (1950) records the abolition of thirst in a patient with diabetes insipidus by decompression of an arachnoid cyst which was compressing hypothalamico-hypophyseal connexions. Likewise the association of hypothalamic lesions with polyuria is well known, and Harris (1948), by implanting electrodes in the hypophyseal stalk, demonstrated in the rabbit that stimulation of this region produced antidiuresis. Kovács *et alii* (1959) have demonstrated, by means of crossed circulations between the heads of two dogs, that there is central nervous control of renal function, albeit of sodium excretion, in such animals.

As the kidney is the organ through which any excess of stored fluid is lost from the body, any or all of the known factors controlling urine formation may be part of the volume-regulating mechanism; but it is not known what part is played, for example, by changes in pressure-flow patterns of the fluids in the glomeruli and tubules and by the various hormones influencing tubular function.

In the present state of knowledge, it is possible only to suggest that between the receptor and the effector mechanisms there is a link which has both nervous and hormonal components. The slowness of the changes observed clinically certainly suggests that non-nervous mechanisms are the limiting agents in speed of response.

PROPERTIES OF A VOLUME RECEPTOR

The concept of a control mechanism containing monitoring receptors has been successful in so many aspects of regulation of bodily processes that it seems likely that the same situation will exist for volume regulation. However, many investigators have found it difficult to describe how a volume receptor could monitor volume so as to assess the individual's own normal volume and deviations from this normal. It has been suggested (Wolf, 1958) that one of the many inextricably associated physical parameters, such as pressure, tension, linear dimension, diffusion gradient, concentration, may be the effective stimulus to the receptor.

In this commentary it has been suggested that the storage mechanism is " open system " in nature. If that is so, one of these difficulties is removed, for there is no need for the volume receptor to assess " normal " volume. The normal volume in such a system is determined by the characteristics of the inflow and outflow mechanisms, and the receptor has only to be sensitive to change of volume. The maintenance of normal volume is the maintenance of a steady state.

Analogy with other physiological regulations suggests that the physical parameters associated with volume most likely to actuate the receptor are, as Bull (1953) has suggested, tension in a stretch receptor or the rate of delivery of some substance to a chemoreceptor. However, his investigations on respiration at varying air pressures and on oxygen and carbon dioxide changes in the blood failed to identify such effective stimuli for volume regulation.

The nature of the effective stimulus for the volume receptor remains unknown.

CONCLUSION

It is to be concluded, therefore, that available data indicate that regulation of the fluid volume of the body exists independently of the regulation of other aspects of the body fluid, such as osmotic pressure. The mechanism by which this regulation is effected is known only in part, and it is necessary to postulate a volume receptor in that mechanism. If, as seems likely, the physics of open systems can be applied to this physiological regulation, then the receptor need be sensitive to change of volume only.

The volume receptor controls the inflow (thirst) and outflow (urine) mechanisms through little-known pathways which have both nervous and hormonal components. Further, the evidence to date suggests that some portion of the vascular volume is monitored, but the location of this region has not been conclusively fixed.

From a philosophical point of view, the present situation is summarized by Wolf (1959) thus :

> While it remains easier to see how drinking or renal excretion affects the body volume than to see the reverse, the conviction that volume does influence thirst and renal excretion contrives to fertilize physiologic researches.

It is to be expected that solution of this problem of volume regulation will contribute greatly to an understanding of the mechanisms leading to œdema and sometimes to dehydration.

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Proceedings of the Royal Australasian College of Physicians

ORDINARY MEETING, 1959

The Ordinary Meeting of the College was held in Canberra from October 15 to 17, 1959. It was attended by 184 Fellows and Members representative of all the Australian States and New Zealand. The President, Professor J. G. Hayden, was in the chair.

College Ceremony

The College Ceremony was held in the Albert Hall on October 16, 1959, in the distinguished presence of the Prime Minister of Australia and Dame Pattie Menzies. An audience of 500 was present. Addresses were given by the President and the Prime Minister.

Presentation of Newly Admitted Fellow and Members

The Censor-in-Chief presented to the President a new Fellow, Professor F. J. Fenner, of Canberra, who had been admitted under the provisions of Article 44; a new Member, Dr. P. L. Bazeley, of Melbourne, who had been admitted under Article 37; and two of the 23 Members successful at the recent Membership examination, Dr. P. E. Hurst, of Perth, and Dr. Wong Hee Ong, of Singapore.

G. R. Rennie Memorial Lecture

Douglas Miller Esq., F.R.C.S., F.R.A.C.S., delivered the G. E. Rennie Memorial Lecture entitled "Artificers of the Golden Bowl". At the conclusion of the Ceremony guests were entertained at supper in the Hotel Canberra.

College Dinner

The College Dinner was held at the Hotel Canberra on the evening of Saturday, October 17. His Excellency Field Marshal Sir William Slim, Governor-General of Australia, attended the dinner in his capacity as an Honorary Fellow of the College. Guests at the dinner were: Mr. J. A. James, representing the President of the Royal Australasian College of Surgeons; Dr. E. Graeme Robertson, President of the Australian Association of Neurologists; Sir John Eccles, President of the Australian Academy of Science; and Professor A. H. Ennor, Dean of the John Curtin School of Medical Research. The toast of the College was proposed by Dr. W. W. S. Johnston, of Melbourne, a Vice-President of the College, and was acknowledged by Dr. K. B. Noad, Censor-in-Chief, on behalf of the President.

Scientific and Clinical Programme

Two scientific sessions, a clinical meeting and a plenary session with the Australian Association of Neurologists were held in the Conference Chamber of the Australian Academy of Science.

First Scientific Session

At the first scientific session on Thursday, October 15, the following contributions were presented.

David B. Pitt, in a paper entitled "Congenital Malformations and Maternal Diet", by David B. Pitt and Patricia E. Samson, stated that nutritional deficiency had been shown by many workers to be teratogenic to the animal embryo. Vitamins of the B group especially appeared to be essential for normal organogenesis. It was also stated that this was consistent with the known general functions of the B vitamins, which acted as intracellular enzymes and promoted rapid cell growth, for example, in the adult hæmatopoietic and gastro-intestinal systems. In the study an attempt had been made to detect deficiencies in the diets of 99 mothers who had borne malformed children. When their estimated diets had been compared with those of a matched control series, statistically significant differences had been found in several groups of malformation, especially cleft lip, congenital heart disease and talipes. No differences had been found in mongolism and spina bifida. The most usual differences had been in protein, calories and B group vitamins (thiamin, riboflavin and niacin). On comparison of the findings with hereditary estimates deduced from twin studies, it appeared that the worst maternal diets were found in those conditions in which genetic factors seemed least important.

In a paper by D. F. J. Halmagyi and H. J. H. Colebatch entitled "Ventilation and Circulation in Experimental and Non-Fatal Drowning", Dr. Halmagyi stated that small quantities (1 to 5 ml. per kilogram) of sea and fresh water were introduced into the trachea of lightly anæsthetized and intubated sheep. Total and alveolar ventilation, arterial oxygen saturation and carbon dioxide tension, cardiac output, "effective" pulmonary capillary flow, and systemic and pulmonary arterial pressures were measured before, and at five and 30 minutes after, the administration of fluid in 13 intact and five vagotomized animals. Five sheep kept on the operating table for a similar period of time but left untreated served as controls. The following changes were observed: (*a*) A gross fall

in arterial oxygen saturation, largely independent of the amount of fluid injected, but somewhat dependent on the chemical composition. It was due to the passage of venous blood through unventilated areas of the lung; consequently, it remained largely unrelieved by the breathing of 100% oxygen. Prior vagotomy prevented this hypoxæmia. (*b*) A marked increase in pulmonary arterial pressure and resistance, largely independent of the amount of fluid injected and unaffected by vagotomy. It was due to constriction of the pulmonary arterioles; pulmonary "capillary" pressure did not change. Ætiologically it appeared unrelated to hypoxia; its mechanism was yet unidentified.

B. C. E. Ashley delivered a paper entitled "Drastic Dietary Reduction of Obesity", by B. C. E. Ashley and H. M. Whyte, in which he reported that obese patients had been starved for up to four weeks without hunger, discomfort or apparent harm. One had been given salty tomato juice to provide an electrolyte intake. All had been given adequate water and vitamins. They had all lost weight rapidly—1 kg. per day in the first week, much less in the second week, and then had continued to lose weight steadily. Metabolic balance studies had shown that there was a loss of up to 2 litres of body water in the first week, and this was restored during the second week. In one patient with a 10 kg. weight loss, after three weeks 7·5 kg. had been fat and 2·5 kg. had been "cells". Nitrogen loss had progressively diminished to about 4 grammes per day after two weeks. "Nilevar" (17 ethyl-19 nortestosterone) had suppressed nitrogen loss and had caused a positive potassium balance at both high and low levels despite the absence of external calories. The author stated that as an initial treatment for obesity the method was useful because (i) patients realized that they could go without food and not feel hungry, (ii) there was a gratifying loss, and (iii) the acceptance of the following 500 Calorie diet was easier. The studies had been designed primarily for their application to anuria. If the patients were to be made theoretically anuric, it would be possible to show how much external water they would need to maintain fluid balance. The amounts needed had been about 500 ml. per day, which supported the current conservative methods of treating anuria. In addition, the effects of protein metabolism and electrolyte changes could be studied more readily in a healthy urinating subject.

Maurice R. Joseph, in a paper entitled "Familial Sarcoidosis", reported the occurrence of sarcoidosis in four siblings of European stock. A fifth sibling had pulmonary tuberculosis. The problem of the ætiology of sarcoidosis was reviewed, and it was suggested that the strongly familial instance of a comparatively rare disease argued in favour of a genetic factor determining that type of response of the individual to possibly a number of ætiological agents, which might include the acid-fast bacillus.

John Read, in a paper entitled "The Assessment of the Distribution of Gas and Blood in the Lungs", reported that after a full inspiration of an argon-air mixture, a continuous record of the changing concentrations of oxygen, carbon dioxide and argon was obtained during expiration by use of the respiratory mass spectrometer. The changing gas concentrations were automatically plotted against expired volume. From the oxygen and carbon-dioxide concentrations at successive points in expiration, the range of ventilation-blood flow ratios throughout the lungs could be obtained. Similarly, the range of alveolar ventilations was obtained from the changing argon concentrations, and the range of pulmonary blood flow by calculation. In 34 normal subjects, both pulmonary ventilation and pulmonary blood flow had become more uneven with advancing age. In 19 patients with emphysema, pulmonary ventilation had always been uneven. In some cases, uneven pulmonary blood flow seemed to "compensate" uneven ventilation. In 17 patients with pure interstitial disease of the lungs, uneven ventilation had been common. Pulmonary blood flow remained even, and the resulting non-uniformity of ventilation-blood flow ratios throughout the lungs constituted an extra burden added to the diffusion defect.

Plenary Session

"Cerebral Vascular Disease" was the subject of a plenary session held with the Australian Association of Neurologists on Saturday, October 17.

In introducing the symposium, L. B. Cox said that vascular disease of the brain was to be considered by a number of physicians and other workers interested in the central nervous system, against a background of physicians with wider interests. Thus it was wisely recognized that the brain was part of an organism, and that involvement of its arteries might be but one aspect of a widespread disorder which affected the human unit. No neurologist, neuro-pathologist, physiologist or chemist, however skilled, could neglect the knowledge contained within general medicine. The subject was so diverse and extensive that it would take many such sessions to cover. But something was to be learnt of its pathology, problems in its diagnosis, its ischæmic attacks and its management. At the end some time would be given to summarizing and coordinating what had been presented. No doubt in discussing pathology, something would be said of causation. That would enable those present to see which diseases affecting the vessels were the most important as social problems, and enable those that were less so to be mentioned so that they were not forgotten. However, the common diseases were likely to have pride of place in the discussion. Diagnosis would be considered in relation to certain valuable methods now in use, especially by way of visualization of the cerebral vessels with radio-opaque substances. Last of all would come the management and treatment of established diseases. Perhaps at some time some ideas which were just emerging as to prevention might be introduced into discussion.

If they thought in terms of the great killing and disabling disorders of their times, vascular disease of the brain would take a position of great prominence. Even in early life they encountered two congenital malformations, the common aneurysm and the less common arterio-venous malformation, each of which might kill by hæmorrhage, and the second might cause socially disabling symptoms such as epilepsy and recurrent headache. Fortunately a significant number of cases of each could now be treated surgically, and revealed by modern X-ray techniques.

Of the less common diseases cerebral periarteritis nodosa, perhaps always a manifestation of allergy, might be helped by modern steroid therapy. The infective diseases with their accompanying endarteritis obliterans had become less prominent, and with the introduction of antibiotics much had been achieved in their control. Rheumatic fever, too, which might have important cerebro-vascular manifestations, might be included with that group. Lastly, there were two conditions which might be combined in the one individual—cerebral atherosclerosis, and those changes in cerebral arteries which might follow hypertension. Destructive through their complications of hæmorrhage and thrombosis, they killed or crippled body and mind in the middle and later ages to a degree that could hardly be computed.

The hypertensive state might be ameliorated by resection of some elements of the central nervous system, or by the various hypotensive drugs; but the atherosclerotic patient presented an insuperable problem, as he might have no hypertension to treat. There was little known about the causation of atheroma, although it was known that atheroma-like lesions might be produced in certain experimental animals by overfeeding them with cholesterol, and that for some reason it was common in those people who ate the most animal fats. The factors involved were by no means simple, and they might hope that to be generally abstemious in diet was one means of prevention.

Such conditions were fundamentally generalized diseases, and it was unlikely that the neurologist or neuro-scientist would contribute greatly to their final defeat. That they involved his field was partly due to the comparative weakness of the cerebral arteries, which had an adventitial coat and a single elastic lamina, which rendered them particularly liable to rupture. Also the vital brain cells, 10,000 million strong, were particularly susceptible to anoxæmia, which easily resulted from thrombosis or narrowing of the cerebral arteries and arterioles. The neurons could not reproduce themselves after birth as could less highly evolved tissues, and on them depended movement and mental health. To have lost one's limbs was an important disability, but to have lost one's mind was to lose one's "self". Perhaps from the researches of those nearest to the fundamentals, the biochemist and the biophysicist, would come that knowledge which would enable physicians to prevent or cure the atherosclerotic and hypertensive patient. Meanwhile it was of value that a symposium such as the present one should be undertaken. It would tell those present whether they had gained any new knowledge, and would remind them how much unknown lay before them.

R. McD. Anderson, in a paper entitled "Pathology of Cerebro-Vascular Accidents", presented the major findings in 265 cases of fatal cerebro-vascular accident. He stated that in 162 of those patients hæmorrhage had been the main finding, and in the other 103 infarction of brain tissue had occurred. When bleeding had occurred primarily into the brain substance (86 cases), preexisting hypertension had been present in all but seven cases. Of those seven patients, three had had leukæmia, three had had arterio-venous malformations, and one had had subacute bacterial endocarditis. Sixty-one ruptured saccular aneurysms had been found in 64 cases of primary subarachnoid bleeding. The age incidence in those cases had been similar to the group in which bleeding had been primarily into the brain substance. Preexisting hypertension had been present in one-third of the cases, and in one-quarter of the cases aneurysms had been multiple. Of the 103 patients with infarction of the brain, relevant cardiac disease had been present in 22. In 12 cases recent myocardial infarction had been present, in six clinical auricular fibrillation associated with thrombus in the auricle, and in four bacterial endocarditis. In one-third of the cases of infarction no total occlusion of a vessel had been found. In some of them a lowered systemic blood pressure appeared to have been responsible for the infarction. In others, particularly earlier cases, inadequate examination of cerebral arteries in the neck probably had caused overlooking of blocked vessels. When the arterial block was extracranial, other arteries had usually been narrowed or the circle of Willis had been abnormal.

In discussing "Difficulties in Diagnosis", K. B. Noad stated Kinnier Wilson's mnemonic for the causes of, and modes of onset of, hemiplegia:

E. Embolism, coming on in seconds
A. Apoplexy (hæmorrhage), coming on in minutes
T. Thrombosis, coming on in hours
I. Inflammation (encephalitis), coming on in days
T. Tumour, coming on in weeks.

The differential diagnosis of embolism, thrombosis and hæmorrhage was discussed. He reported that embolism was usually distinguished by its sudden onset and by the discovery of the source of an embolus, such as atrial fibrillation or myocardial infarction. The importance of differentiating thrombosis from hæmorrhage was pointed out, because of the increasing use of anticoagulants in treatment. Thrombosis was usually of slower onset, and was frequently preceded by minor focal episodes of monoplegia, dysarthria, aphasia or paræsthesia. Cerebral hæmorrhage, of more rapid onset, was usually associated with severe headache and vomiting and rapidly deepening unconsciousness. Neck rigidity was commonly present, and the finding of blood-stained cerebro-spinal fluid under increased pressure was almost diagnostic. The difficulty of differentiating between cerebral vascular disease and cerebral tumour was discussed. Ischæmia of the "watershed" areas might produce symptoms mimicking tumour. A full investigation was often necessary to decide. The use of the ophthalmodynamometer in the diagnosis of internal carotid occlusion was mentioned. In conclusion, the diagnosis of subdural hæmatoma was briefly discussed. The importance of a careful history, the waxing and waning of symptoms and the pressure of ptosis, dilated pupil or ocular palsy from the third nerve compression were stressed.

"Cerebral Ischæmic Attacks" were discussed by John Billings in the symposium. He reported that focal cerebral ischæmia most often followed obstruction of an internal carotid or cerebral artery, or of the basilar artery, or of one or more of the great vessels arising from the arch of the aorta in the "aortic arch syndrome". It was occasionally encountered in obstruction of the larger cerebral arteries. The obstructions were usually the result of atherosclerosis, but might follow trauma and embolism. The cerebral ischæmic attacks might occur as a series of almost identical focal disorders of brain function. The patient might have a few or even some hundreds of attacks over a period of weeks or months, each lasting from a few minutes to a few hours, and leaving little or no residual sign. In the presence of obstruction of the internal carotid artery, there might be transient monocular blindness on the affected side, paresis of a limb or possibly of both limbs on the opposite side of the body, accompanied at times by paræsthesiæ or dysphasia. If obstruction was to be confined to one vertebral artery, the ischæmic episodes might comprise vertigo and nystagmus, sometimes ipsilateral deafness, and in other cases ipsilateral ataxia or contralateral weakness and sensory loss. With failure of the basilar circulation the weakness might first be on one side of the body and then on the other, whilst spastic or flaccid quadriplegia might occur. There might be episodes of bilateral deafness, of gross ataxia, of paralysis of ocular movement, of hemianopia or complete blindness and sometimes of loss of consciousness.

"Management of Cerebral Vascular Disease" was discussed by W. Burke. He reported that in recent years the major advance in the management of cerebral vascular disease had been in the use of long-term anticoagulant therapy for the prevention of cerebral

ischæmic attacks. In the syndromes of intermittent insufficiency of the basilar and carotid arteries, anticoagulants would usually bring about a marked reduction in the number of cerebral episodes. Long-term anticoagulant therapy had also been recommended in cases of progressive infarction in the vertebral basilar territory, for multiple small strokes or for thrombo-embolic cerebral episodes associated with cardio-vascular lesions. Some authors had favoured bishydroxycoumarin (" Dicoumarol "). Dr. Burke said that they considered a prothrombin index range from 30% to 60% as effective. Most of the intracranial hæmorrhages complicating anticoagulant therapy had occurred in patients with a prothrombin index persistently below 30%, and hypertension was also a hazard. A series of 40 patients with basilar and carotid syndromes on anticoagulant therapy had been reported. Clinical experience had shown that the ischæmic attacks in those cases might have been dramatically reduced by anticoagulant therapy, and a prothrombin index range from 50% to 65% had been found adequate. Among the patients presented were some who had relapsed immediately after cessation of anticoagulant therapy, even though their prothrombin index on treatment had not been below 50%. The oral anticoagulant phenindanedione (" Dindevan ") had been the most widely used agent in this series. Recent work had suggested that those anticoagulants had a lipid-clearing effect not directly related to the degree of prothrombin depression, and such effects, by limiting the " sludging " in the smaller cerebral vessels, might reduce the cerebral attacks. The occurrence of those cerebral ischæmic episodes depended on the adequacy of the collateral circulation. Cardiac disease might precipitate a breakdown of that collateral flow, and hypotensive drugs also might be contra-indicated in the treatment of the elderly arteriosclerotic patient with cerebral ischæmic episodes. There might also be scope for endarterectomy or other surgical measures on the carotid in cases of recent occlusion of the internal carotid in the neck, especially before cerebral infarction had occurred.

In the " Concluding Remarks " of the symposium, E. Graeme Robertson said that widening therapeutic possibilities increased diagnostic responsibilities, yet the nature of the cerebral lesion was often speculative. As an illustration, embolism was considered to be the most probable of numerous possible causes of a cerebral lesion accompanying a pulmonary arterio-venous malformation and multiple hereditary hæmorrhagic telengiactasis. With P. Ebeling he had investigated the diagnostic value of carotid compression by using electroencephalographic and electrocardiographic recording. The test had no exact diagnostic significance, although focal symptoms usually indicated arterial narrowing, and the absence of effect suggested that another cause of the clinical picture was more likely. Compression of the more, or the less, abnormal carotid artery might have the greater effect, and the cerebral dysfunction might begin on the side compressed or contralaterally. Unless a carotid sinus reflex was excluded, wrong deductions might be made. The lability of the circulation endowed by the circle of Willis was shown when the left posterior cerebral artery failed to fill during vertebral angiography. However, with coincidental left carotid compression, the left posterior and middle cerebral arteries (both from the carotid artery) filled via a posterior communicating artery, while the right posterior cerebral artery failed to fill. Its territory, and that of both anterior cerebral arteries, were, under those conditions, supplied from the right carotid system. The importance of systemic blood pressure was shown in a patient with stenosis of the right carotid artery and atheroma of other arteries. After femoral catheterization to demonstrate the basilar system, a large hæmatoma formed in the groin, and ischæmia of the left cerebral hemisphere occurred. Finally, other iatrogenic lesions were discussed, including cerebral ischæmic lesions accompanying the use of hypotensive drugs, and hæmorrhage associated with the use of anticoagulants. Recorded results suggested that anticoagulants should be used in cases of intermittent cerebral ischæmia, yet failure suggested the need for detailed statistical analysis.

Second Scientific Session

At the second scientific session on Saturday, October 17, the following contributions were presented.

D. W. Piper, in a paper entitled " The Control of Gastric Secretion ", reported that peptic ulceration was considered to be due to the action of pepsin and acid. The function of acid was to produce the correct pH for pepsin to exert its maximal proteolytic activity. Previously, attention had been directed towards the neutralization of the acid. However, to reduce peptic activity the concentration of the acid had to be markedly reduced, whereas pepsin was related to peptic activity in an approximately linear fashion. Also, if the effect of anticholinergic drugs on gastric secretion was studied, it would be found that with increasing anticholinergic suppression of secretion there would be a rise in pepsin concentration. A study was made of the methods of inactivation of pepsin. Initially, the effect of the sulphated polysaccharides was studied, and later a series of adsorbents. The sulphated polysaccharide " Ebimar " was found to inhibit peptic activity; it appeared to act on the substrate, and had little or no action on pepsin. It was less active at high substrate levels, and was not influenced by pH changes in the range 2 to 4. Of the adsorbents tested, only charcoal and aluminium hydroxide gel were found to be powerful adsorbents of pepsin. Aluminium hydroxide gel acted directly on the pepsin and was less active at high pepsin concentrations, but was not influenced by the substrate concentration. It was less active at high pH levels. The greatest disadvantage of the sulphated polysaccharide group was that they acted on the substrate levels as would be found after a meal. When aluminium hydroxide gel was used clinically, and its adsorbent effect on pepsin was more important than its pH effect.

R. Motteram, in a paper entitled " Myelosclerosis ", said that a series of patients suffering from myelosclerosis had been investigated, and the findings obtained from marrow biopsy, serum uric acid estimation, alkaline phosphatase activity of leucocytes and intravenous radioactive iron injection were described. When the marrow showed a gross increase in megakaryocytes, the serum uric acid levels were raised above normal to a maximum of 15 mg. per 100 ml. Normal uric acid levels were found when the megakaryocytes were not significantly increased. The leucocyte alkaline phosphatase levels fell into two distinct groups. One was in the above-normal range as seen in polycythæmia vera, and the other showed the below-normal values typical of chronic myeloid leukæmia. There was a rapid clearance of injected ^{59}Fe from the plasma, the average rate being four times the normal. Surface radioactive counting showed that the ^{59}Fe went mainly to the enlarged spleen. Plasma iron values were within normal limits, so that there was a greatly increased iron turnover. That should have resulted in increased erythropoiesis, but the delivery of tagged cells to the peripheral blood averaged only about 50% of normal. It was therefore postulated that

many of the red cells produced were grossly defective and either failed to be delivered to the blood or existed therein only for a short period.

In a paper entitled " Abnormal Activity of Clearing Factor and its Inhibitor in Coronary Artery Disease, and the Effect of Long-Term Anticoagulants ", by Paul J. Nestel and M. L. Mashford, delivered by Paul J. Nestel, it was reported that clearing factor was an enzyme which appeared in the blood after the ingestion of fats or after an injection of heparin. It hydrolysed the triglycerides of chylomicra to soluble fatty acids, thereby clearing the turbidity of plasma. An inhibitor to that system had also been isolated from plasma. The inhibitor was partly adsorbed to blood platelets, which were removed when plasma was separated at conventional centrifugal speeds. Platelet-rich plasma and platelet-poor plasma were therefore used. Clearing factor and inhibitor activity were measured in four groups of subjects matched for age and sex. One group comprised matched controls, and the other three groups were patients who had had a myocardial infarction several months previously. Of those, one group had received long-term coumarin-type anti-coagulants (" Marcoumar ") and the second group bi-weekly heparin therapy, and the third group were left untreated. Clearing activity was significantly diminished in the untreated group and in the " Marcoumar "-treated group. The group receiving heparin did not differ from the controls. Increased inhibitor activity was demonstrated in all three groups of patients.

In a paper entitled " Cutaneous Manifestations in Polyarteritis (Periarteritis) Nodosa with Report of a Case with Livedo Reticularis ", John C. Belisario stated that the basic lesion of polyarteritis nodosa appeared to be of the nature of an inflammatory, commonly allergic, swelling of the blood vessel wall and was a non-specific hypersensitivity response to a variety of antigens or stimuli. The associated symptoms included pyrexia, malaise, divers neurological symptoms, hypertension, abdominal pains, muscle and joint pains, paræsthesiæ, hæmaturia, œdema, insomnia, sweating, pupura, jaundice, progressive weakness, divers scarlatiniform, erysipeloid or macular to papular or vesiculo-bullous eruptions, and also livedo reticularis. Ecchymoses due to rupture of a weakened arterial wall might be followed by gangrene, which could even affect the bones and gastro-intestinal tract. The skin was affected in approximately 25% of cases, the essential lesions being cutaneous and subcutaneous nodules recurring in groups or crops, sometimes along the course of an artery. If they were to ulcerate, the appearance would be strongly suggestive of clinical evidence of the diagnosis. The ulceration would exhibit a peculiar, small, relatively superficial, punched-out, necrotic appearance in the centre of a fawn to brownish-tinted area on varying degrees of scaly erythema. Dr. Belisario said that he had observed six such cases in which he was able to make a correct diagnosis from the clinical appearance in the last four seen. Five occurred in women (in four the lesions were on the legs below the knee and in one on the ankles). One occurred in a man and affected both the legs and ankles. In 1935, Goldschlag (now of Sydney) and Chiwalibogowski were the first to describe a persistent reticular livedo in a boy, aged five years. Since then a number of cases had been reported. Lyell and Church (1954) and others had indicated that there was a cutaneous type, characterized by livedo reticularis, ulceration, muscle pains and œdema, which had comprised the disease and was more chronic in nature. They had distinguished this from a visceral type, in which the skin had been involved inconsistently and incidentally by exanthemata, ecchymoses and gangrene. Subcutaneous nodules were found to be common to both forms. Dr. Belisario reported a case in which the typical ulceration of the lower extremities and generalized livedo reticularis had been present, and both it and two other cases were illustrated by 35 mm. colour-slide projections.

In a paper entitled " Ataxia, Telangiectasia and Sino-Pulmonary Disease ", John Beveridge stated that a report had been made of three patients, two of whom were brothers, suffering a combination of symptoms and signs which had appeared distinctive enough to be designated a syndrome. The features were: (i) progressive disease of the central nervous system, consisting of difficulty with balance and writhing movements of the upper limbs, head and trunk; (ii) recurrent and then chronic diseases of paranasal sinuses and bronchi; (iii) telangiectases involving bulbar and palpebral conjunctivæ, ears, neck and flexures of elbows and knees; (iv) skin atrophy, especially of the bridge of the nose, cheeks and forehead. It was assumed that the familial factor was also an important one.

Clinical Meeting

At a clinical meeting on Friday, October 16, the following contributions were delivered: " Benign Idiopathic Pericarditis ", by C. H. Scott Reed; " Beriberi Heart Failure ", by J. R. E. Fraser; " Œdema and Hypokalæmia in a Patient with Carcinoma of the Lung ", by Margaret Henderson; " Histiocytosis in the Diagnosis of Subacute Bacterial Endocarditis ", by Professor J. G. Hayden; " Blood Dyscrasia from Petrol Containing Benzol ", by John McLean.

VISIT TO JOHN CURTIN SCHOOL OF MEDICAL RESEARCH

Fellows and Members visited the John Curtin School of Medical Research on the afternoon of Friday, October 16, at the invitation of the Dean of the School, Professor A. H. Ennor.

OFFICE BEARERS

The following have been elected office bearers of the College for the term 1960–1962, and will take office on May 25, 1960, at the annual meeting of the College: *President:* T. M. Greenaway. *Vice-Presidents:* F. Ray Hone, H. Maynard Rennie and E. H. Roche (New Zealand). *Censor-in-Chief:* K. B. Noad. *Honorary Secretary:* R. L. Harris. *Honorary Treasurer:* Bruce Hall.

MEMBERSHIP

Honorary Fellowship. At the Meeting of the College held on October 14, 1959, the President admitted *in absentia* to Honorary Fellowship of the College Sir Arthur Sims, in recognition of his great services to medicine in New Zealand and Australia, by the foundation and endowment in perpetuity of the Sims Commonwealth Travelling Professorships.

Admission of Fellow. After election by the General Body of Fellows on October 16, 1959, Frank John Fenner, of Canberra, was admitted to Fellowship of the College *under Article* 44.

Admission of Members. The following candidates, who were successful at examinations held in Melbourne in October, 1959, were admitted to Membership on October 13, 1959: V. J. Barron, F. M. Elliott, Patrick Harvey, J. R. Johnson and D. W. O'Gorman Hughes, of New South Wales; John M. Court, E. A. Dodge, Joan M. Handley, W. C. Heath, H. Hillman, David McCredie, Ian Maddocks, E. N. O'Brien and G. I. Vidor, of Victoria; S. A. Birdseye and G. M. Kneebone, of South Australia; J. B. Cope, D. J. Hodges, L. W. L. Jackson and Miles Murphy, of Queensland; P. E. Hurst, of Western Australia; R. B. Langley, of New Zealand; Wong Hee Ong, of Singapore. Under the special provisions of Article 37, J. D. Reid, of New Zealand, was admitted to Membership by the Vice-President for the Dominion on September 16, 1959, and P. L. Bazeley, of Victoria, was admitted on October 13, 1959.

Honours. The following Fellows have been the recipients of honours bestowed by Her Majesty the Queen: Sir Charles Bickerton Blackburn, of Sydney, Knight Commander of St. Michael and St. George; Sir Edward Ford, of Sydney, Knight Bachelor; Sir William Johnston, of Melbourne, Knight Bachelor; R. G. Ch. de Crespigny, of Adelaide, Officer of the Most Excellent Order of the British Empire.

Obituary. Council records with regret the deaths of Dr. John K. Adey, O.B.E., and Dr. M. D. Silberberg, of Victoria, and of Dr. H. K. Fry, D.S.O., of South Australia, who were Foundation Fellows of the College; of Dr. W. P. MacCallum, C.B.E., D.S.O., M.C., E.D., of New South Wales, who was a Fellow of the College; of Dr. Colin W. Ross, of New South Wales, and Dr. Graeme Larkins, of Victoria, who were Members of the College.

Membership. The College now has a roll of 11 Honorary Fellows, 345 Fellows and 601 Members.

GENERAL

Gifts. Dr. J. V. Duhig, of Brisbane, has presented a painting of the exterior of the College building at 145 Macquarie Street, which had been done by Mr. Frank Sherrin in 1941. Books for the Library have been received from Dr. Douglas Anderson, Dr. T. Clive Backhouse, Dr. J. C. Belisario, Mrs. Wilfred Fairfax, Dr. Bryan Gandevia, Dr. Keith Kirkland, Dr. C. T. Hand Newton, The Queensland Institute of Medical Research, Professor H. N. Robson, St. Thomas' Hospital, Sydney Hospital, Dr. David C. Wallace, and the Wellcome Historical Library.

Bequest by the Late Dr. Eric Susman. The College has received with appreciation a bequest of £5000, made by the late Dr. Eric Susman for the award of a prize to be known as the Eric Susman Prize, to be awarded annually at the discretion of Council to a Fellow or Member for the best contribution to the knowledge of any branch of internal medicine.

Travelling Scholarship in Medicine or the Allied Sciences. The Travelling Scholarship in Medicine for 1960 has been awarded to Dr. R. B. I. Morrison, of New Zealand.

Appointment of College Representatives. Council has appointed the following to represent the College: Dr. E. H. Roche on the Auckland Medical Research Foundation; Dr. Morvyn Williams on the Post-Graduate Study Leave Selection Committee of the Division of Hospitals, Department of Health, New Zealand; Dr. James Isbister on the Conjoint Board of the New South Wales Branch of the British Medical Association, to advise regarding the drawing up of a scheme of accreditation of hospitals in New South Wales.

Research Advisory Committee. The Research Advisory Committee has been reappointed for the term concluding at the time of the Annual Meeting in 1961. This Committee is as follows: Professor Lorimer Dods (Chairman), Dr. Douglas Stuckey (Honorary Secretary), Dr. C. G. McDonald, Dr. S. A. Smith, Professor C. R. B. Blackburn, Sir Edward Ford, Sir Macfarlane Burnet, Sir John Eccles, the Honorary Secretary and the Honorary Treasurer.

The Senior Censor for the Dominion. Dr. J. F. Landreth has been reappointed as Senior Censor for the Dominion for the period 1959–1961.

Jubilee Fund. The Jubilee Fund, established and launched at the College Meeting in October, has been in the first instance directed to Fellows and Members in Australia, and at a later date will be directed to Fellows and Members in New Zealand and to certain outside individuals and organizations. This appeal will culminate at the time of the Silver Jubilee of the College in 1963.

Sir Arthur Sims Commonwealth Travelling Professor. Professor John McMichael, of the Post-graduate Medical School, London, who will be touring Australia and New Zealand as Sims Commonwealth Travelling Professor in 1960, will arrive in Perth on March 20. He will thereafter visit Perth from March 20 to 26, Melbourne from March 27 to April 2, New Zealand from April 2 to May 3, Sydney from May 3 to 17, Hobart from May 17 to 21, Melbourne from May 21 to June 4, Adelaide from June 4 to 10, and Brisbane from June 10 to 16. He will leave from Sydney on June 17. He will attend the Annual Meeting of the College in Melbourne from May 25 to 28.

Future Meetings of the College. The venue of future meetings of the College is as follows. 1960: Annual Meeting, Melbourne, at which a plenary session will be held with the Endocrine Society of Australia; Ordinary Meeting, Sydney, where a plenary session will be held with the Laennec Society. 1961: Annual Meeting, Perth, where a plenary session will be held with the Gastro-Enterological Society.

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